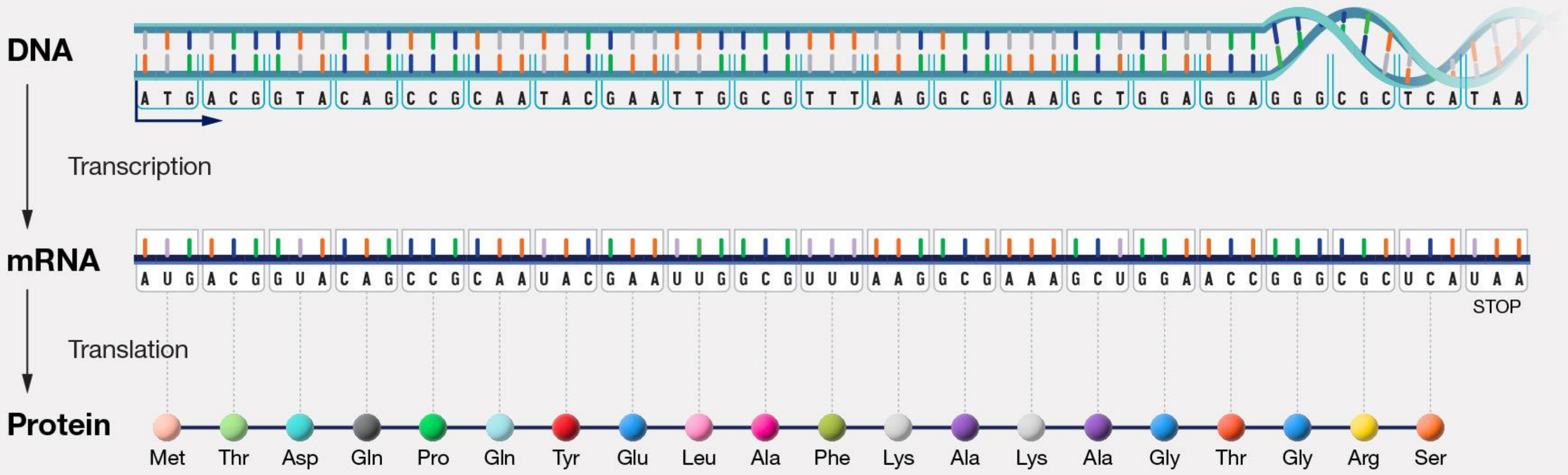
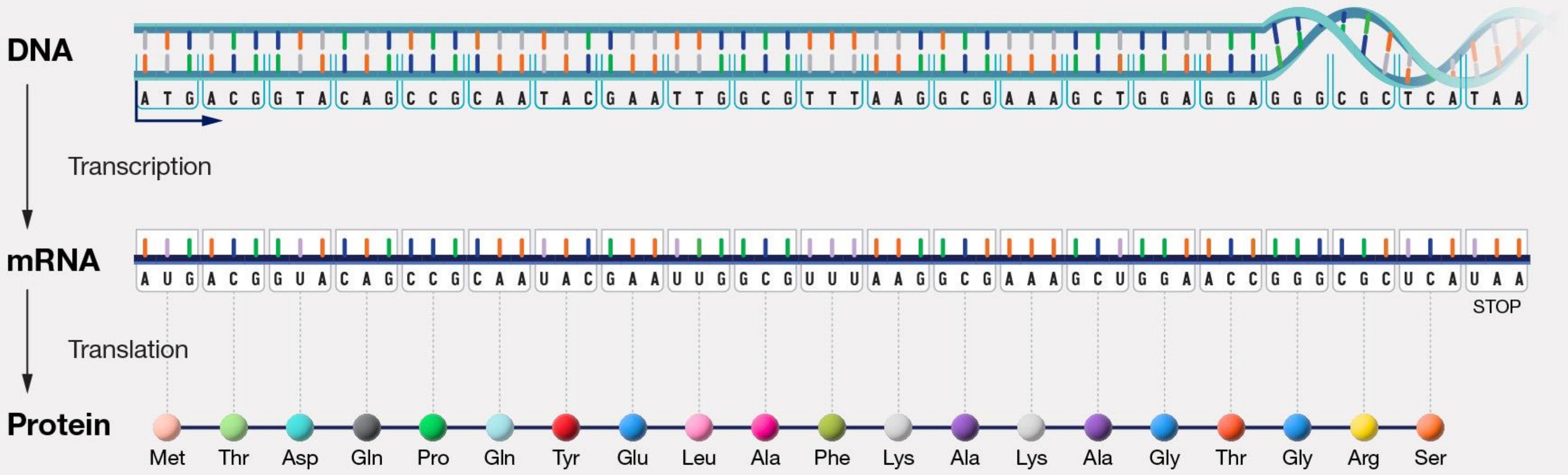
Trascrizione e traduzione



Fabrizio Mafessoni / Trieste 28-10-2024

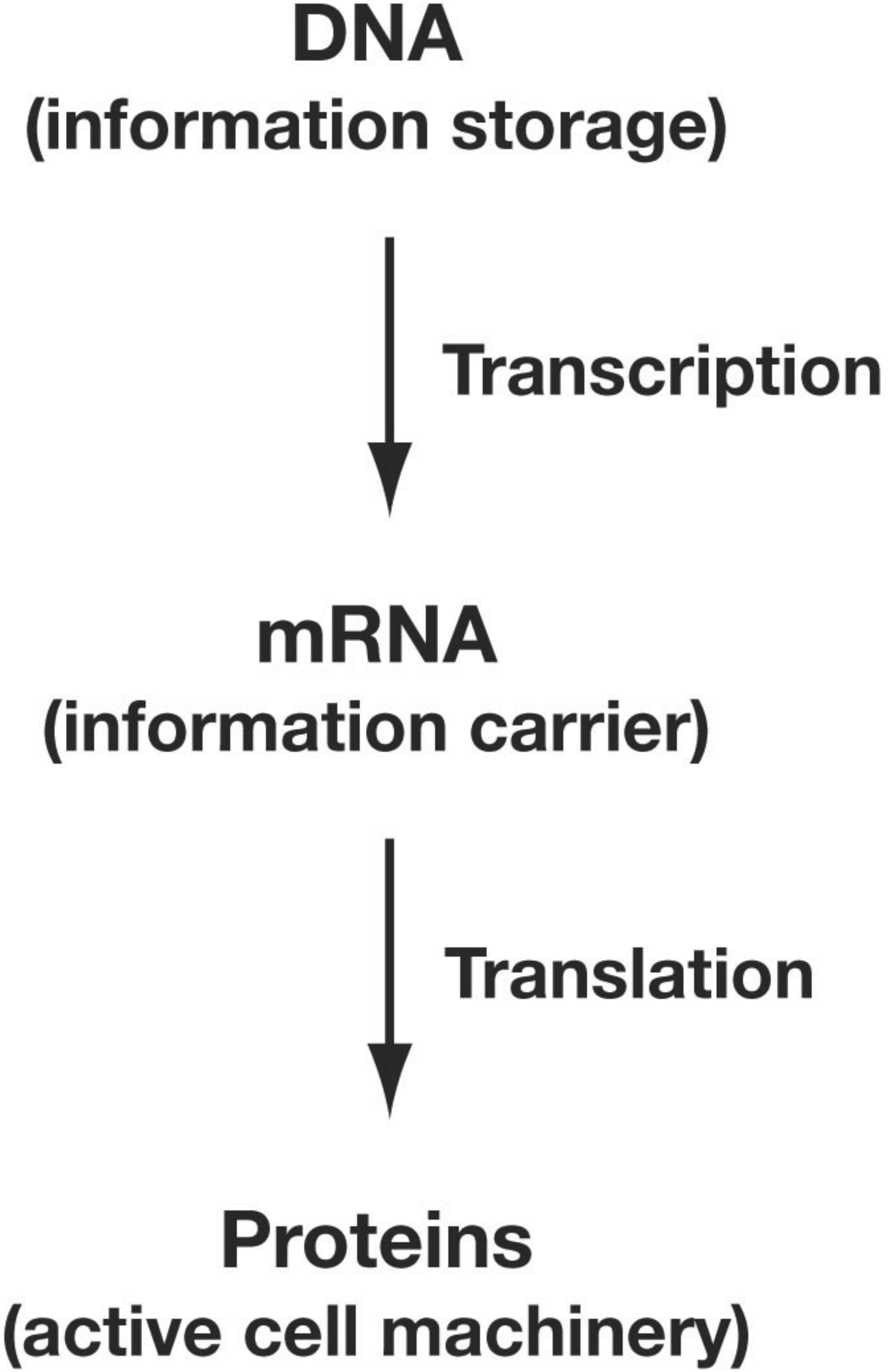
Il dogma centrale della biologia cellulare

Francis Crick, 1958



Il dogma centrale

- Il DNA codifica per l'RNA
- L'RNA codifica per le proteine



DNA
(information storage)

Transcription

mRNA
(information carrier)

Translation

Proteins
(active cell machinery)

Le tappe fondamentali sono universali

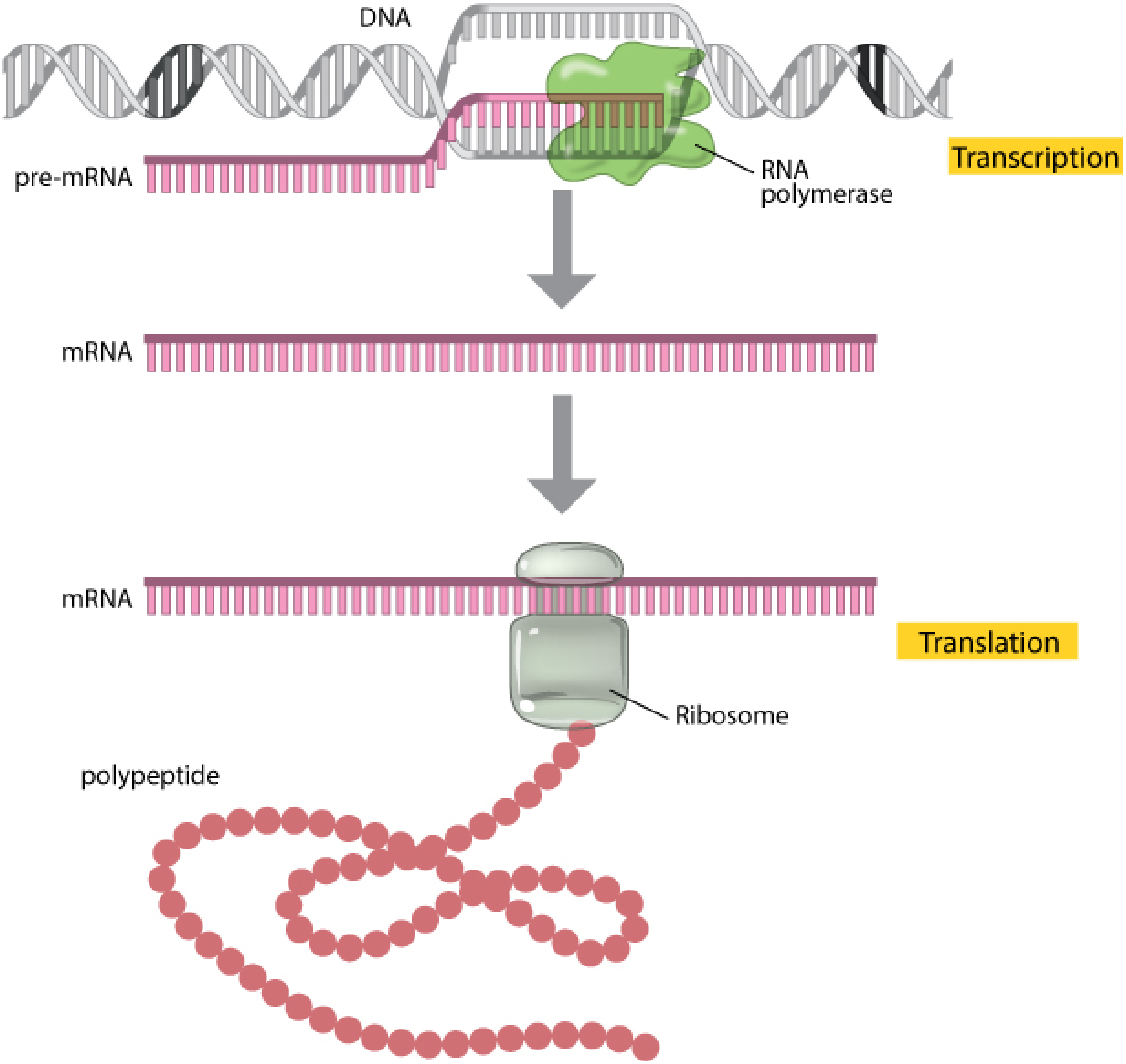
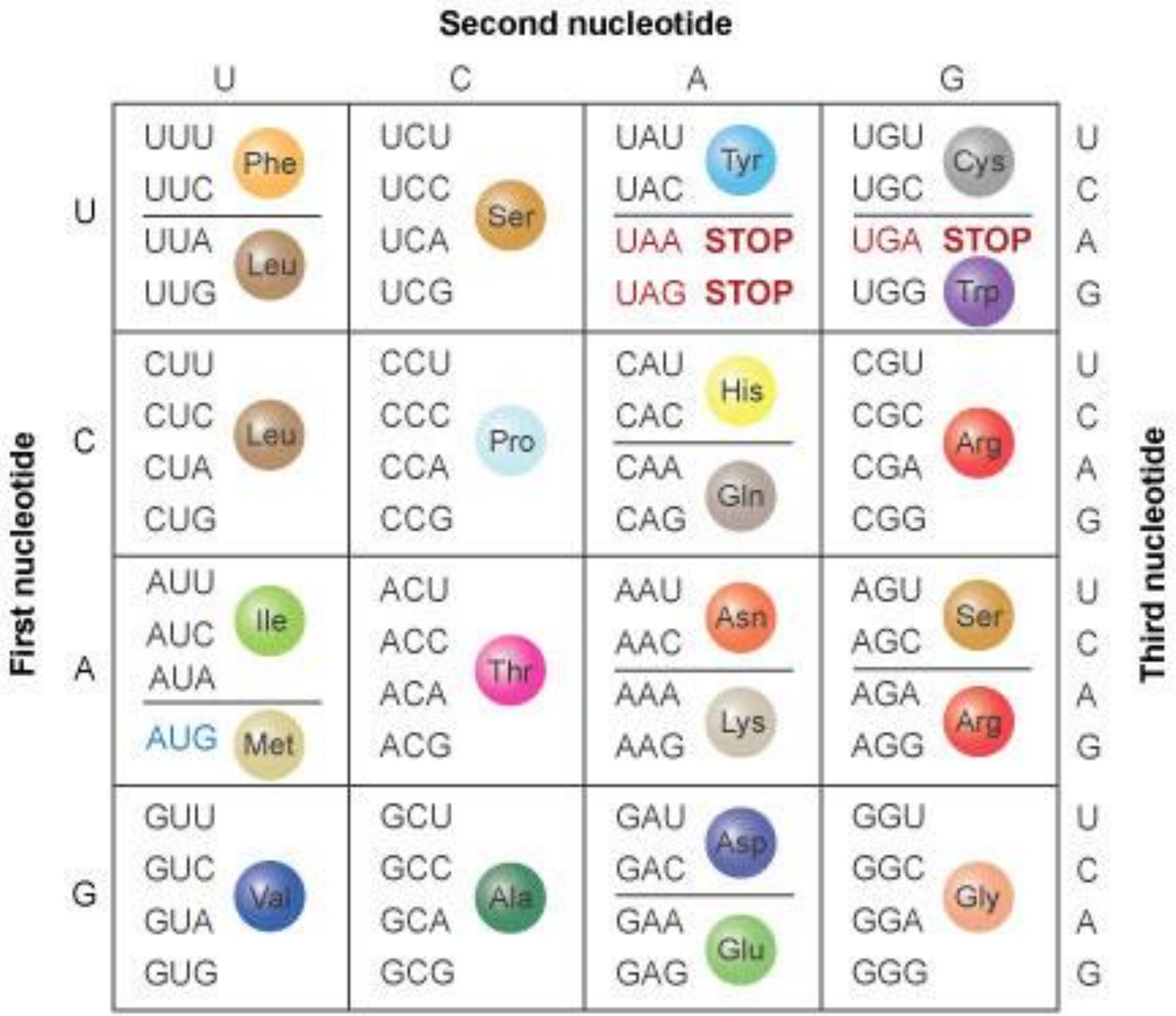


Figure 1: A gene is expressed through the processes of transcription and translation.
During transcription, the enzyme RNA polymerase (green) uses DNA as a template to produce a pre-mRNA transcript (pink). The pre-mRNA is processed to form a mature mRNA molecule that can be translated to build the protein molecule (polypeptide) encoded by the original gene.

Il codice genetico



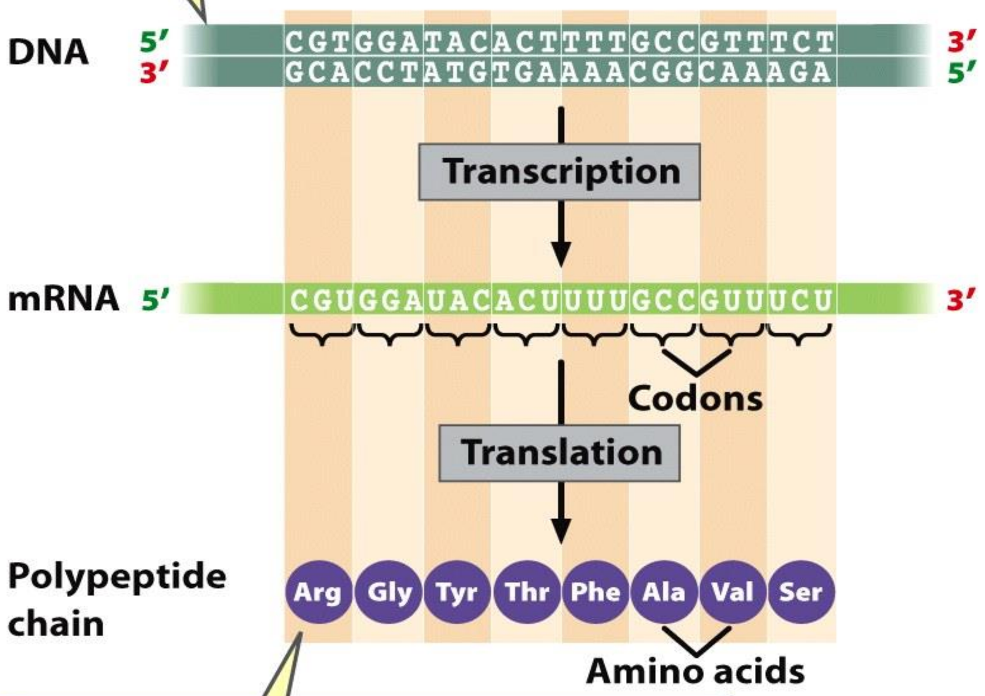
	Second nucleotide								
First nucleotide	U		C		A		G		Third nucleotide
U	UUU	Phe	UCU	Ser	UAU	Tyr	UGU	Cys	U
	UUC		UCC		UAC		UGC		C
	UUA	Leu	UCA		UAA	STOP	UGA	STOP	A
	UUG		UCG		UAG	STOP	UGG	Trp	G
C	CUU	Leu	CCU	Pro	CAU	His	CGU	Arg	U
	CUC		CCC		CAC		CGC		C
	CUA		CCA		CAA	Gln	CGA		A
	CUG		CCG		CAG		CGG		G
A	AUU	Ile	ACU	Thr	AAU	Asn	AGU	Ser	U
	AUC		ACC		AAC		AGC		C
	AUA		ACA		AAA	Lys	AGA	Arg	A
	AUG	Met	ACG		AAG		AGG		G
G	GUU	Val	GCU	Ala	GAU	Asp	GGU	Gly	U
	GUC		GCC		GAC		GGC		C
	GUA		GCA		GAA	Glu	GGA		A
	GUG		GCG		GAG		GGG		G

Trascrizione

- **Trascrizione procariotica**
- L'RNA polimerasi
- Origini e promoters procariotici
- Fasi della trascrizione
- Segnali di terminazione
- Prodotti della trascrizione
- **Trascrizione eucariotica**
- RNA polymerasi
- Promoters eucariotici

- Enhancers
- Fasi della trascrizione eucariotica
- Terminazione
- RNA e modificazioni
    - Lo spliceosoma
    - Talassemia e RNA splicing delle globine
    - Modificazioni di mRNA, tRNA

1 A continuous sequence of nucleotides in the DNA…



2 …codes for a continuous sequence of amino acids in the protein.

Conclusion: With colinearity, the number of nucleotides in the gene is proportional to the number of amino acids in the protein.

Figure 14.1
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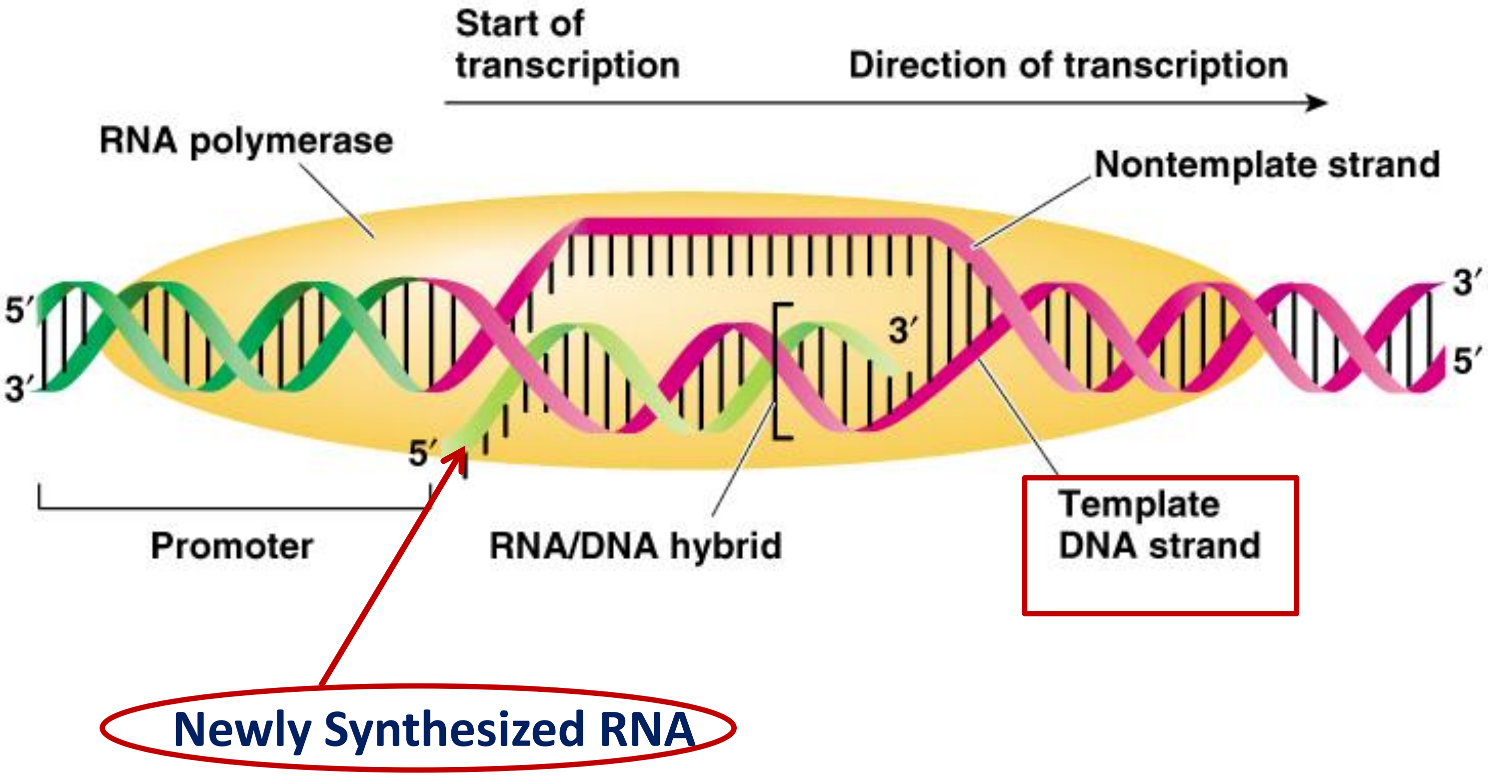
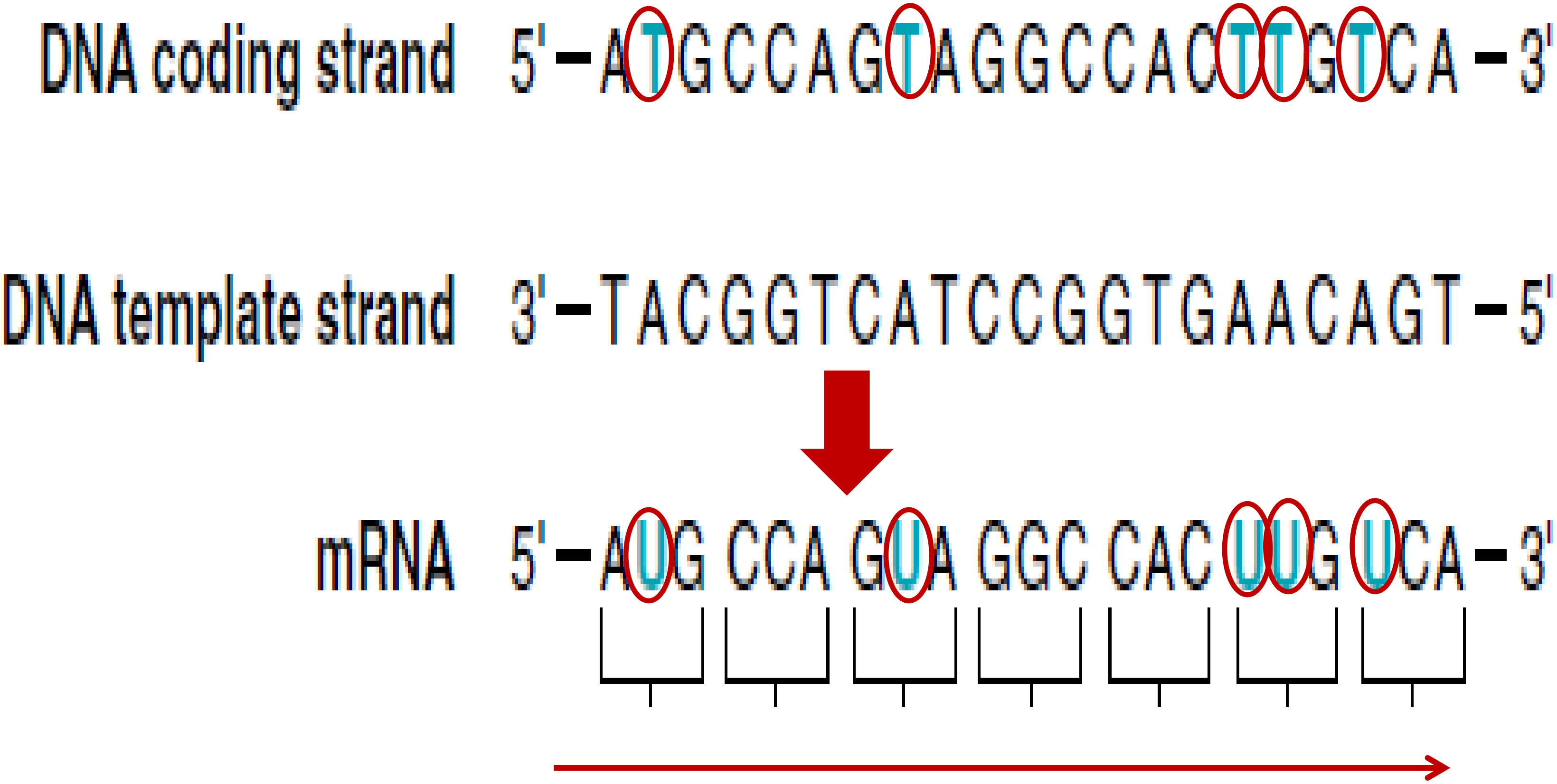
Trascrizione: sintesi di una molecola di RNA a partire da uno dei due strand di DNA tramite RNA Polymerasi.



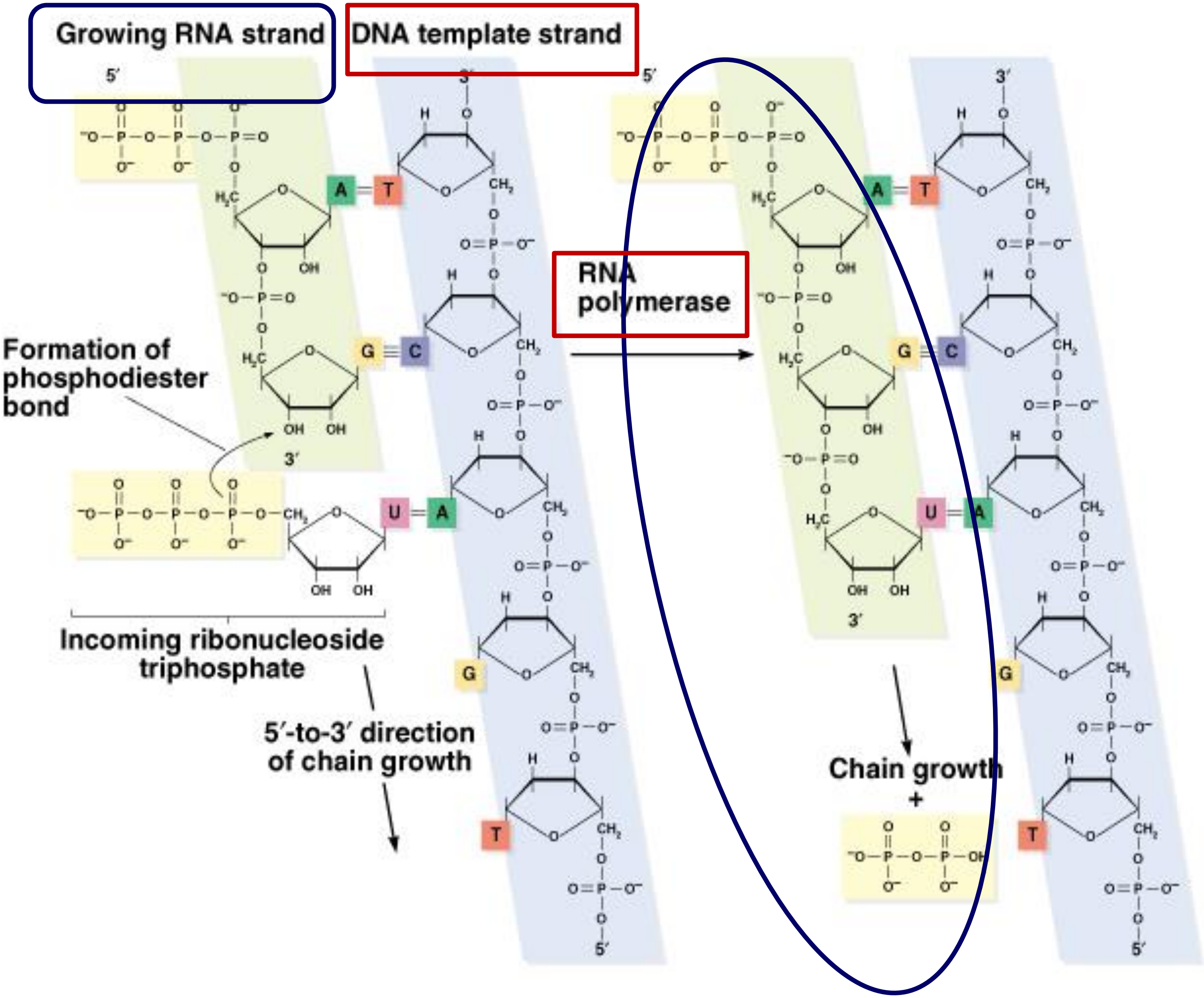


DNA coding strand 5'-ATGCCAGTAGGCCACTTGTCA-3'

DNA template strand 3'-TACGGTCATCCGGTGAACAGT-5'

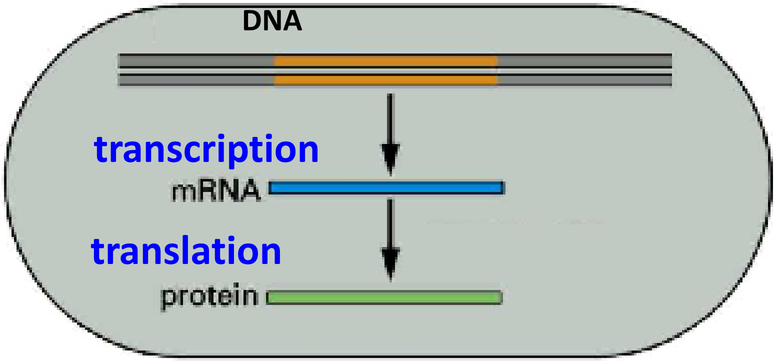
mRNA 5'-AUG CCA GUA GGC CAC UUG UCA-3'

L’enzima central e’ l’RNA polimerasi

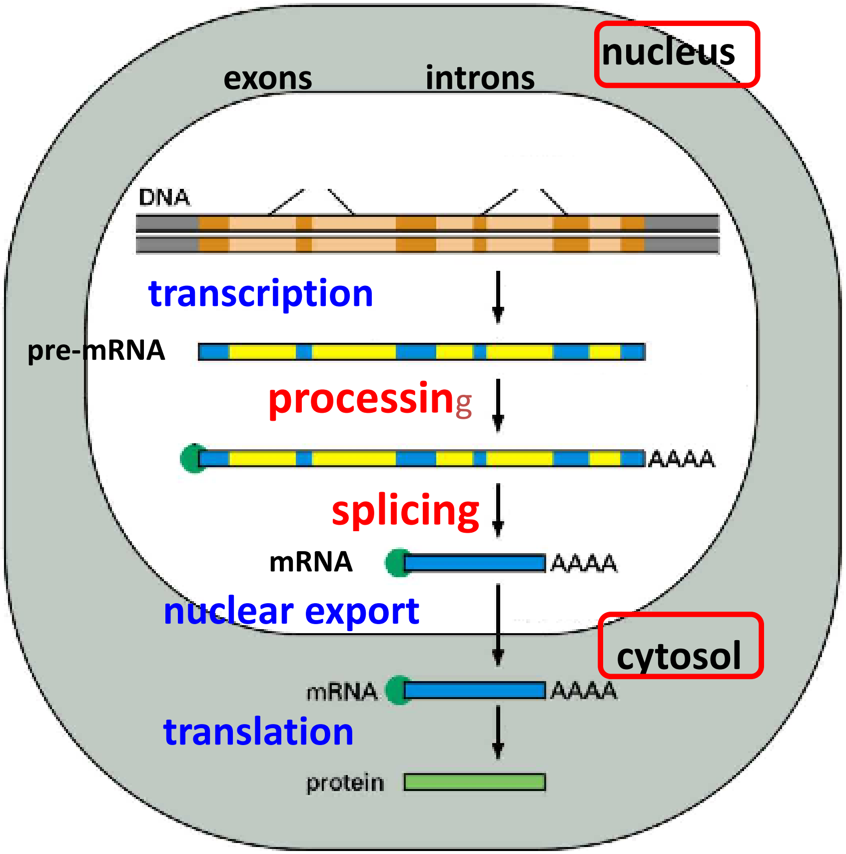


Negli eucarioti trascrizione e traduzione sono separate nello spazio e nel tempo

Procarioti


DNA
transcription
mRNA
translation
protein

Eucarioti


nucleus
exons
introns
DNA
transcription
pre-mRNA
processing
AAAA
splicing
mRNA
AAAA
nuclear export
cytosol
mRNA
AAAA
translation
protein

RNA Polimerasi

- L’RNA polimerasi e’ **DNA-dependente**
  - L’ RNA polymerasi procariotica e’ una proteina con subunita’ multiple di ~480kD.

RNA Polymerasi

$$\boxed{(NMP)_n + NTP \rightarrow (NMP)_{n+1} + PPi}$$

1. Non necessita' primers per la polimerizzazione.
2. Richiede DNA per l'attivita' ed e' piu attiva con un template di DNA a doppio filamento.
3. 5' → 3' synthesis.
4. Richiede Mg^{2+} per l'attivita'.
5. Manca attivita' di 3' → 5' esonucleasi e il tasso di errore e' di circa 10^{-4} - 10^{-5}.

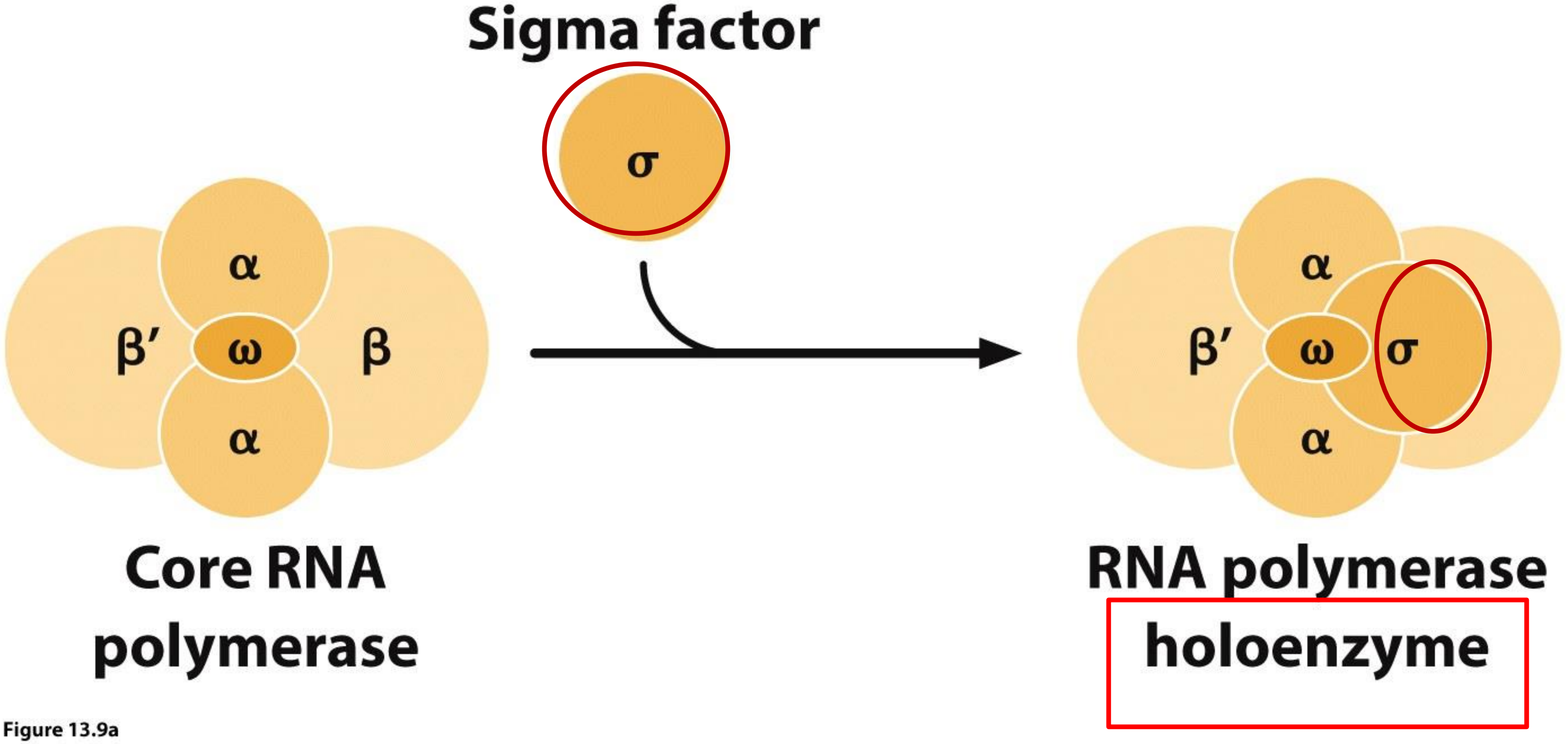


Figure 13.9a
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RNA Polymerasi di *E. Coli*

L'oloenzima della RNA-polymerasi in *E.coli* consiste di 5 differenti subunita': $\alpha_2\ \beta\ \beta'\ \omega\ \sigma$

Subunit	**MW**	**Function**
α	**36.5 KD**	**Determines the DNA to be transcribed**
β	**150 KD**	**Catalyzes polymerization**
β'	**155.5 KD**	**Binds & open DNA template**
σ	**70 KD**	**Recognizes the promoter for synthesis initiation**
ω	**11 KD**	**Subunit packing**

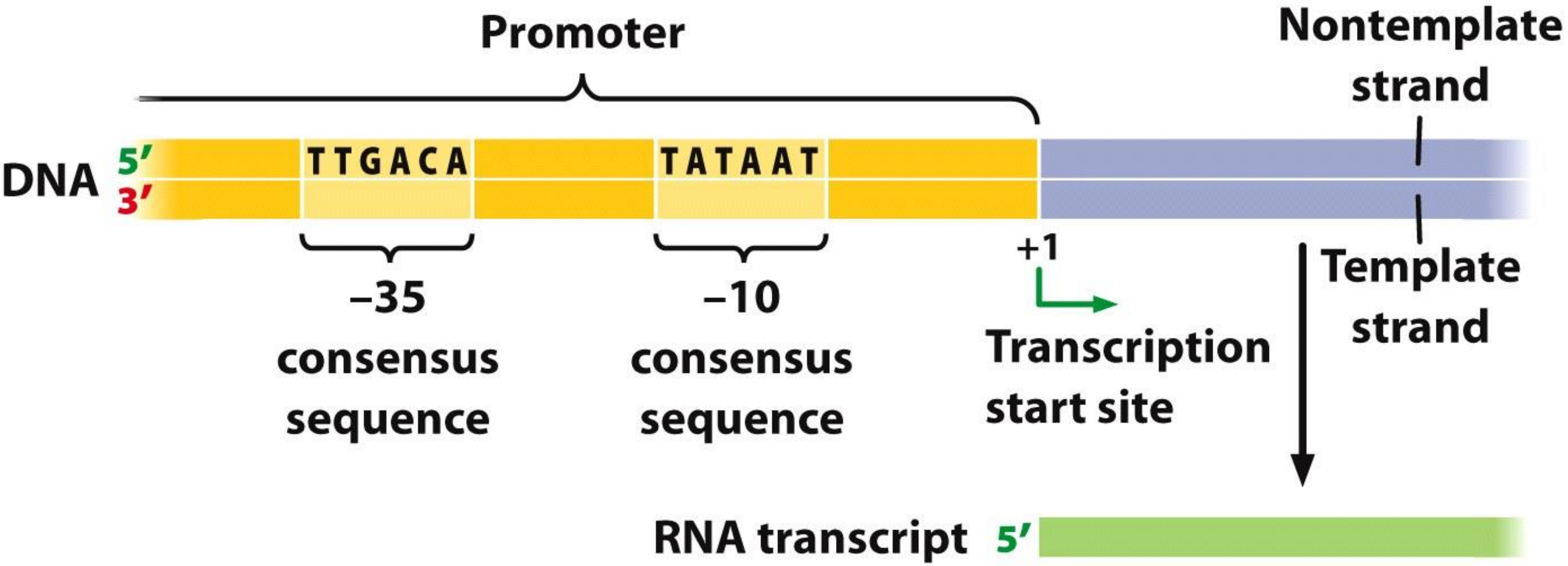

Figure 13.11
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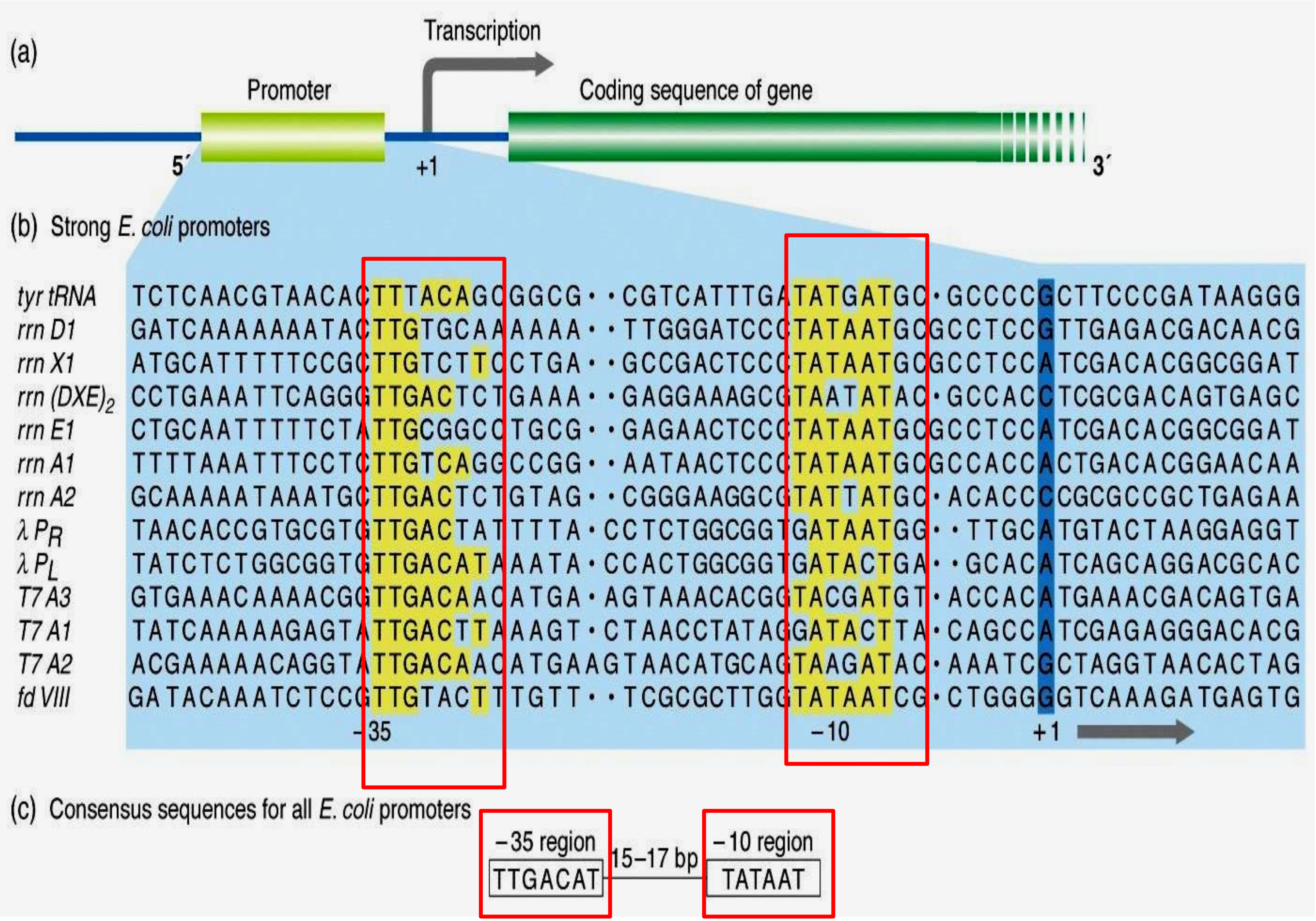
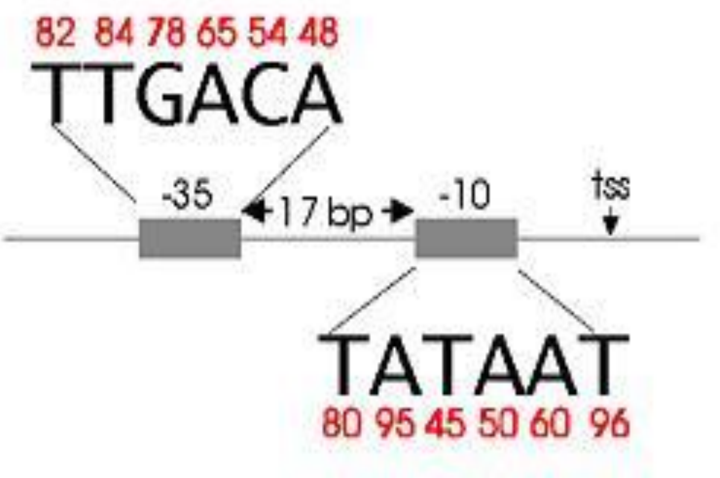

(a)
Transcription
Promoter
Coding sequence of gene
5´
+1
3´
(b) Strong E. coli promoters
tyr tRNA TCTCAACGTAACACTTTACAGCGGCG··CGTCATTTGATATGATGC·GCCCCGCTTCCCGATAAGGG
rrn D1 GATCAAAAAAATACTTGTGCAAAAAA··TTGGGATCCCTATAATGCGCCTCCGTTGAGACGACAACG
rrn X1 ATGCATTTTTCCGCTTGTCTTCCTGA··GCCGACTCCCTATAATGCGCCTCCATCGACACGGCGGAT
rrn (DXE)2 CCTGAAATTCAGGGTTGACTCTGAAA··GAGGAAAGCGTAATATAC·GCCACCTCGCGACAGTGAGC
rrn E1 CTGCAATTTTTCTATTGCGGCCTGCG··GAGAACTCCCTATAATGCGCCTCCATCGACACGGCGGAT
rrn A1 TTTTAAATTTCCTCTTGTCAGGCCGG··AATAACTCCCTATAATGCGCCACCACTGACACGGAACAA
rrn A2 GCAAAAATAAATGCTTGACTCTGTAG··CGGGAAGGCGTATTATGC·ACACCCCGCGCCGCTGAGAA
λ PR TAACACCGTGCGTGTTGACTATTTTA·CCTCTGGCGGTGATAATGG··TTGCATGTACTAAGGAGGT
λ PL TATCTCTGGCGGTGTTGACATAAATA·CCACTGGCGGTGATACTGA··GCACATCAGCAGGACGCAC
T7 A3 GTGAAACAAAACGGTTGACAACATGA·AGTAAACACGGTACGATGT·ACCACATGAAACGACAGTGA
T7 A1 TATCAAAAAGAGTATTGACTTAAAGT·CTAACCTATAGGATACTTA·CAGCCATCGAGAGGGACACG
T7 A2 ACGAAAAACAGGTATTGACAACATGAAGTAACATGCAGTAAGATAC·AAATCGCTAGGTAACACTAG
fd VIII GATACAAATCTCCGTTGTACTTTGTT··TCGCGCTTGGTATAATCG·CTGGGGGTCAAAGATGAGTG
−35
−10
+1
(c) Consensus sequences for all E. coli promoters
−35 region
TTGACAT
15–17 bp
−10 region
TATAAT

Struttura dei promoter batterici

TATA-Box / Pribnow box

- **Regione di 6 nucleotides (5'- TATAAT-3') centrata circa 8-10 nucleotide alla sinistra del sito di inizio della trascrizione.**



Sequenza -35bp

- **Una seconda sequenza di consenso (5'- TTGACA-3'), centrata circa 35basi prima**

Fasi

1. Promoter binding
2. Apertura del DNA
3. Inizio della catena di RNA
4. Elongazione
5. Terminazione

Trascrizione nei procarioti

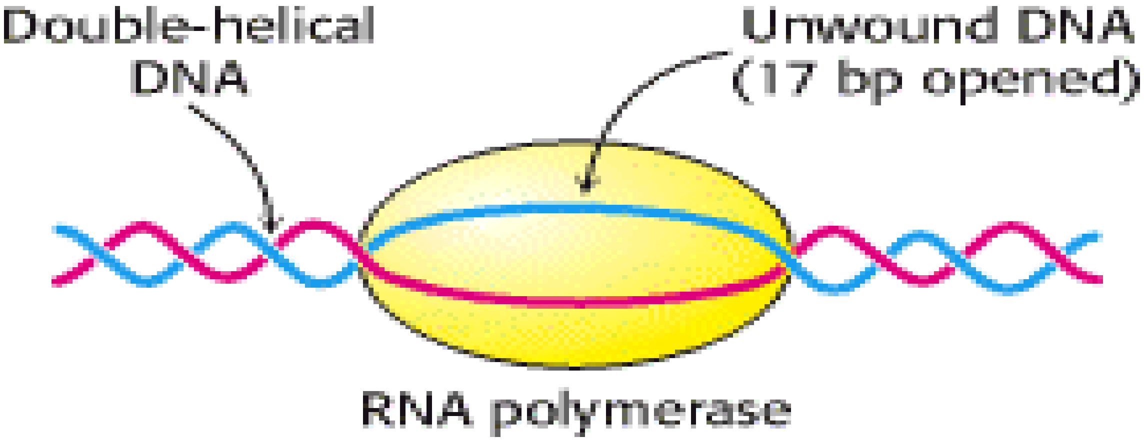
- **Inizio**: L'RNA-polimerasi riconosce il **promoter** e l'inizio della trascrizione.
- **Elongazione**: il filamento di RNA cresce.
- **Terminazione**: L'RNA-polymerasi ferma la sintesi e l' **RNA nascente** si separa dal template di DNA.

Inizio della trascrizione ai promoter

Il processo di elongazione e’ molto simile/conservato tra procarioti ed eucarioti ma inizio e terminazione differiscono

Inizio

- L'RNA-polimerasi riconosce la regione *TTGACA* (sequenza -35), e scivola fino alla regione *TATAAT* (sequenza -10), e poi apre il DNA a doppia elica (duplex).
- La regione aperta e' di circa 17 bp.



- Il primo nucleotide del trascritto (RNA) e’ sempre una purina trifosfato. GTP e’ piu’ comune di ATP.
- La struttura pppGpN-OH rimane sul trascritto finche’ la sintesi dell’RNA e’ completa.
- Le tre molecule formano il complesso di inizio della trascrizione.

RNA-pol ($\alpha_2\beta\beta'\sigma$) - DNA - pppGpN- OH 3′

- **Nessun primer e’ necessario per la sintesi dell’ RNA.**

- **La subunita’ σ si stacca dalla RNA-polymerasi una volta che il primo legame 3′,5′-phosphodiestere si forma.**

- **Il core enzyme si muove lungo il DNA entrando nella fase di elongazione (o di allungamento).**

Elongazione

- **Il rilascio della subunita' σ causa un cambio conformazionale del core enzyme. Il core enzyme scivola sul DNA verso il 3′ terminale.**
- **NTPs liberi sono aggiunti sequenzialmente al 3′ -OH del filament di RNA nascente.**

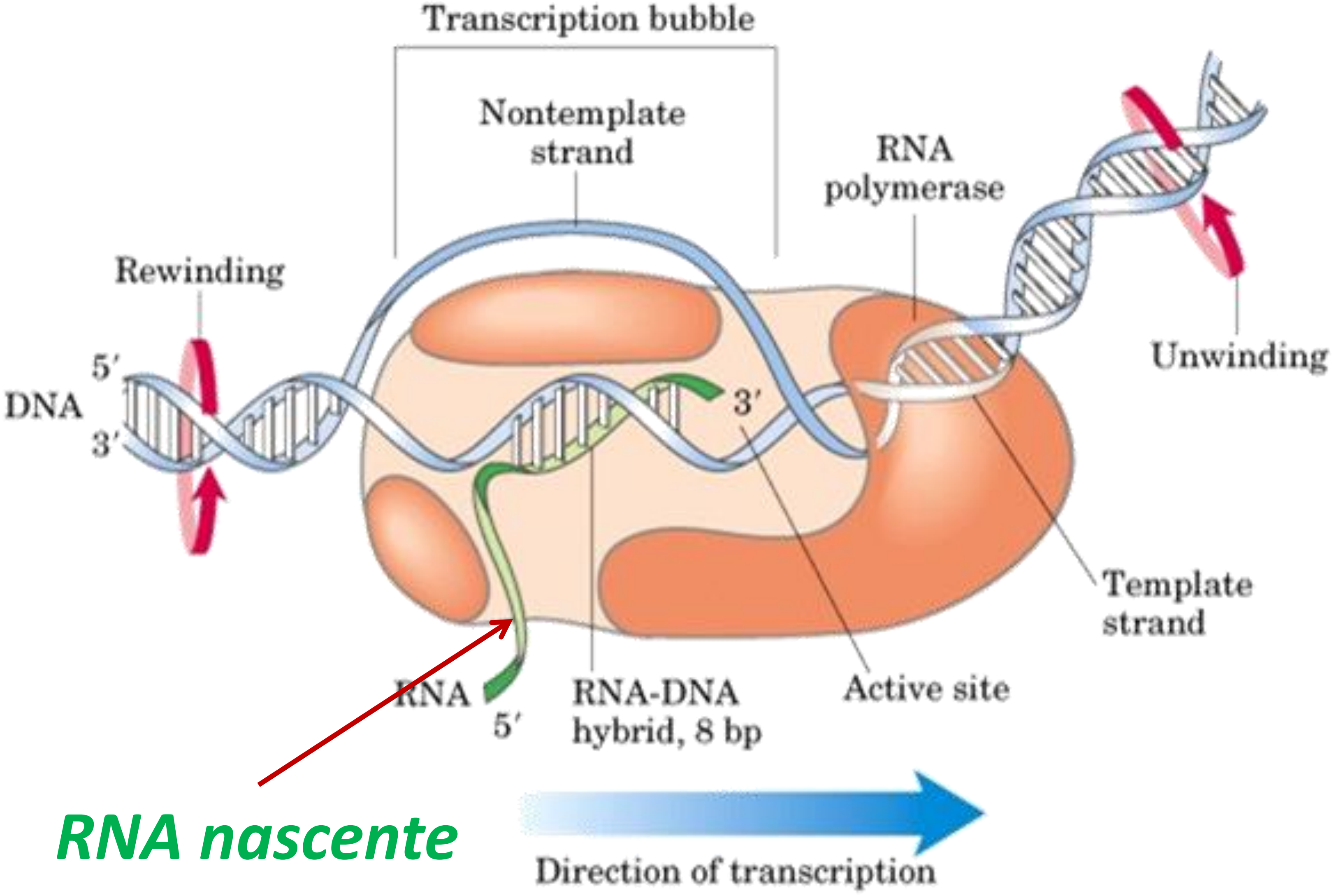
$$(NMP)_n + NTP \longrightarrow (NMP)_{n+1} + PPi$$

RNA strand **substrate** **elongated RNA strand**

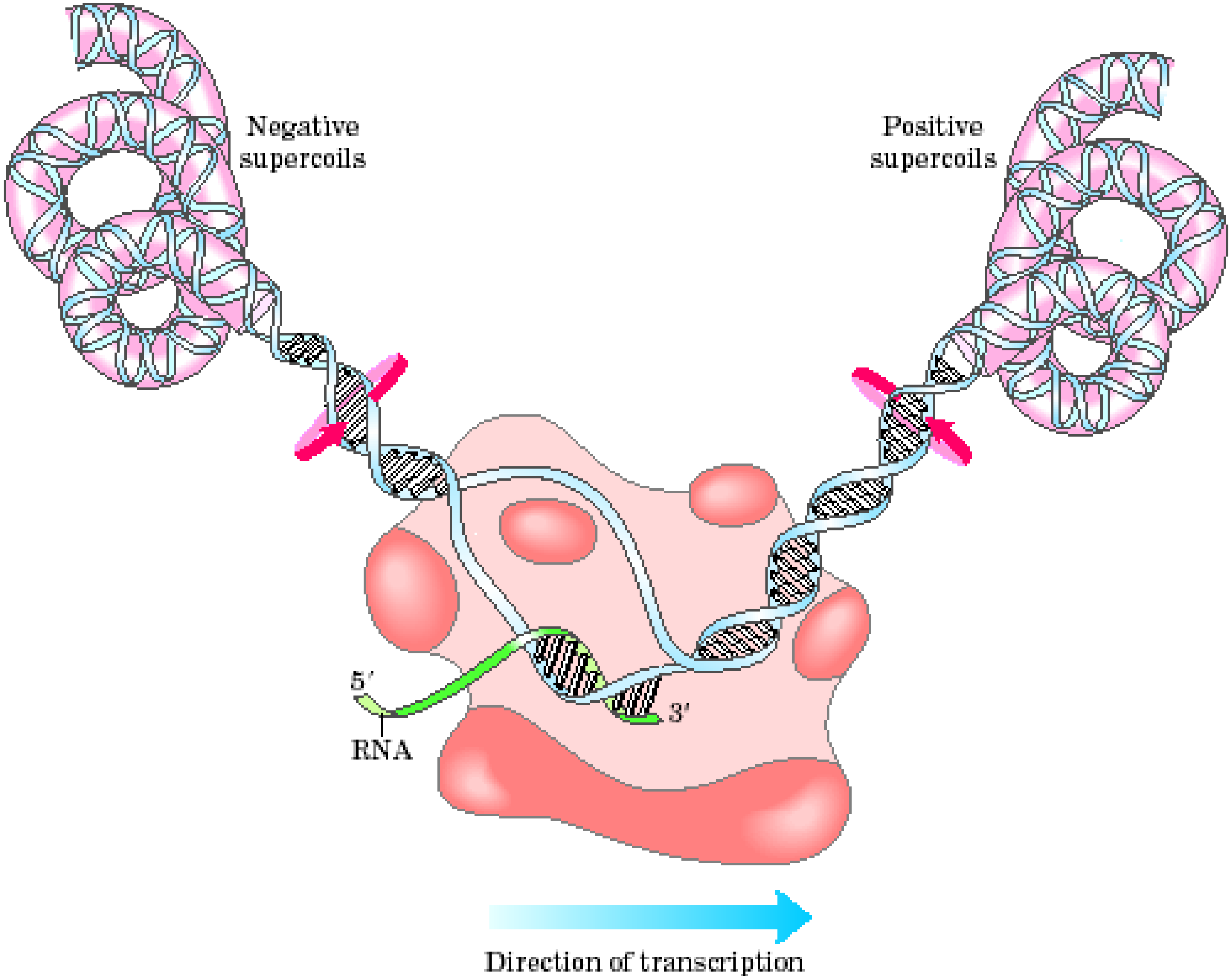
- **L’RNA-polymerasi, il segment di DNA di ~40nt e il RNA nascente formano un complesso chiamato bolla trascrizionale.**

- **Il segmento 3′ dell’ RNA nascente ibridizza col DNA, e il termine ′5’ si estende fuori dalla bolla trascrizionale mentre la sintesi continua.**

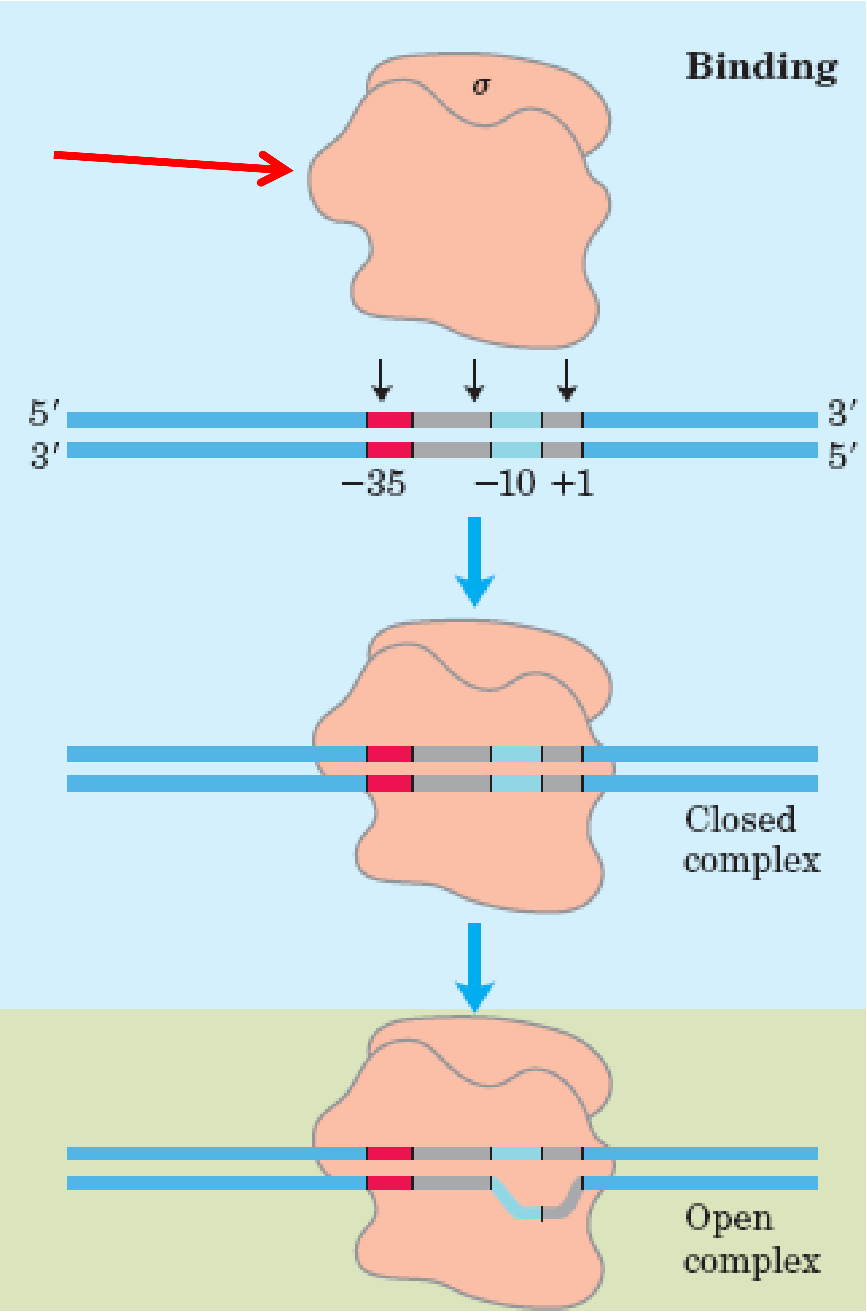
La bolla di trascrizione

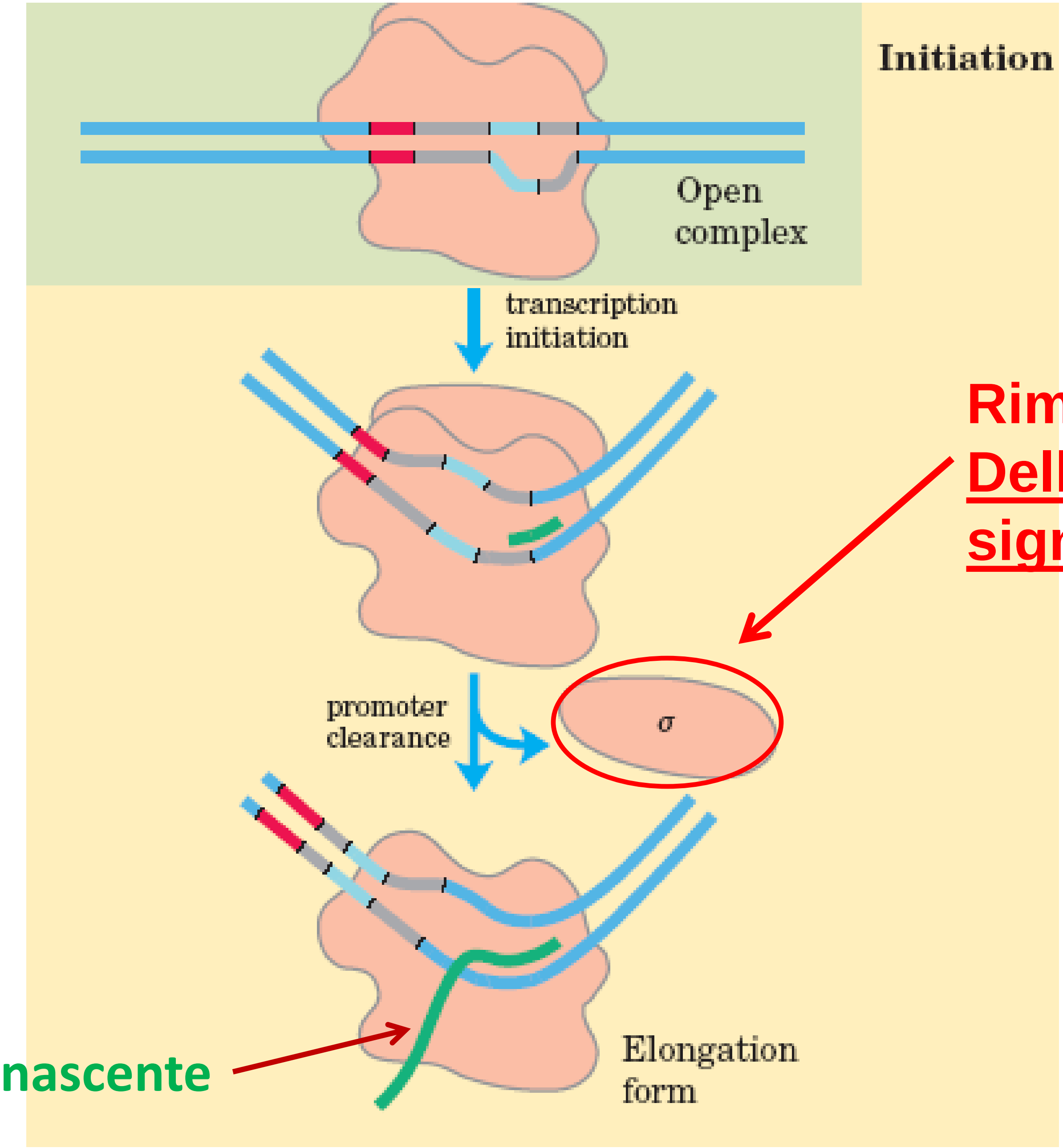


RNA nascente


Negative supercoils
Positive supercoils
5′
3′
RNA
Direction of transcription

RNA Polimerasi





Rimozione Della subunita’ sigma

RNA nascente

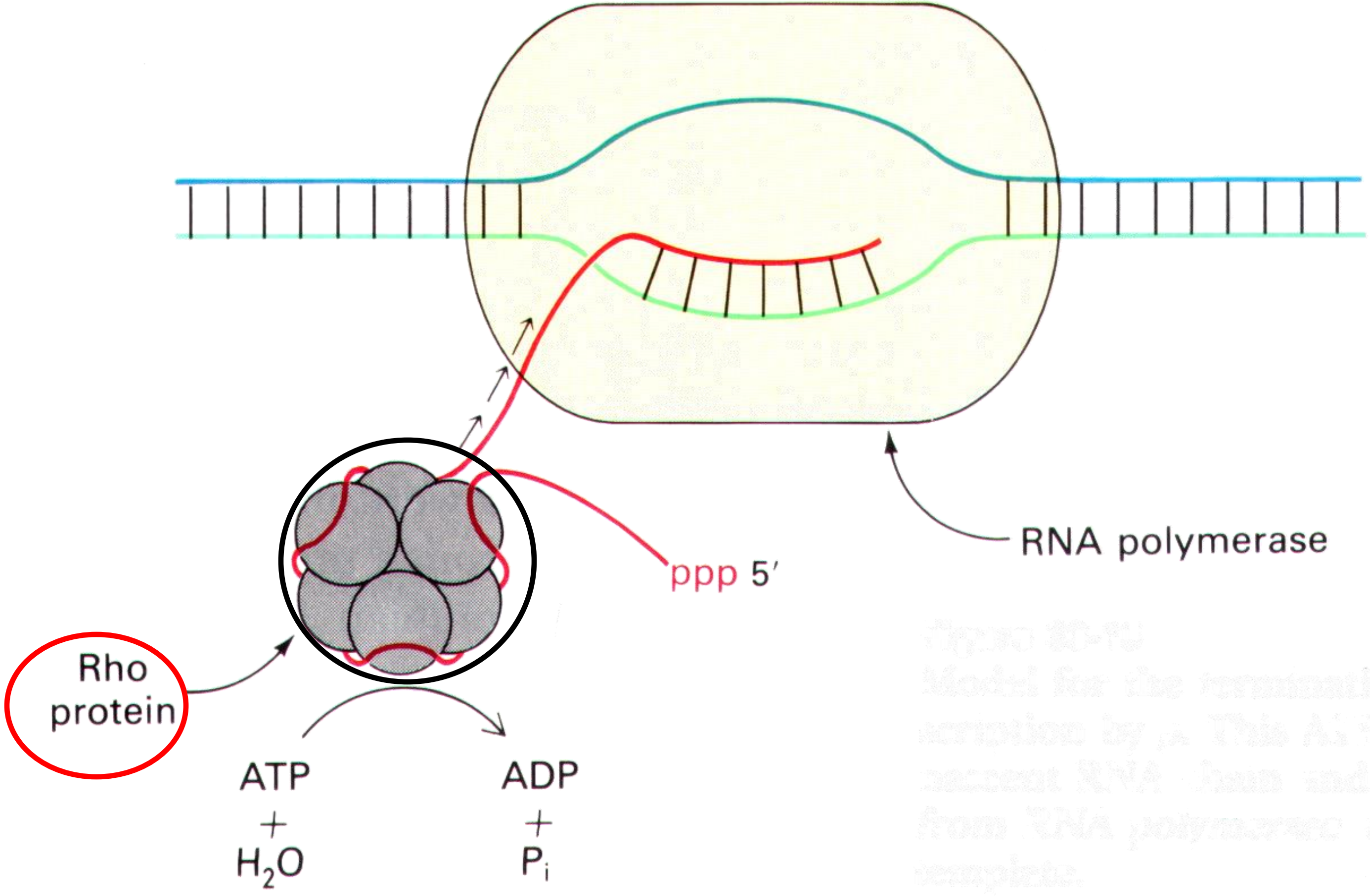
Terminazione

- L’ **RNA Polymerasi** si ferma sul DNA. Il trascritto si stacca dal complesso di trascrizione.

- La **terminazione** occorre in 2 modi:

ρ -dependente o ρ -independente.

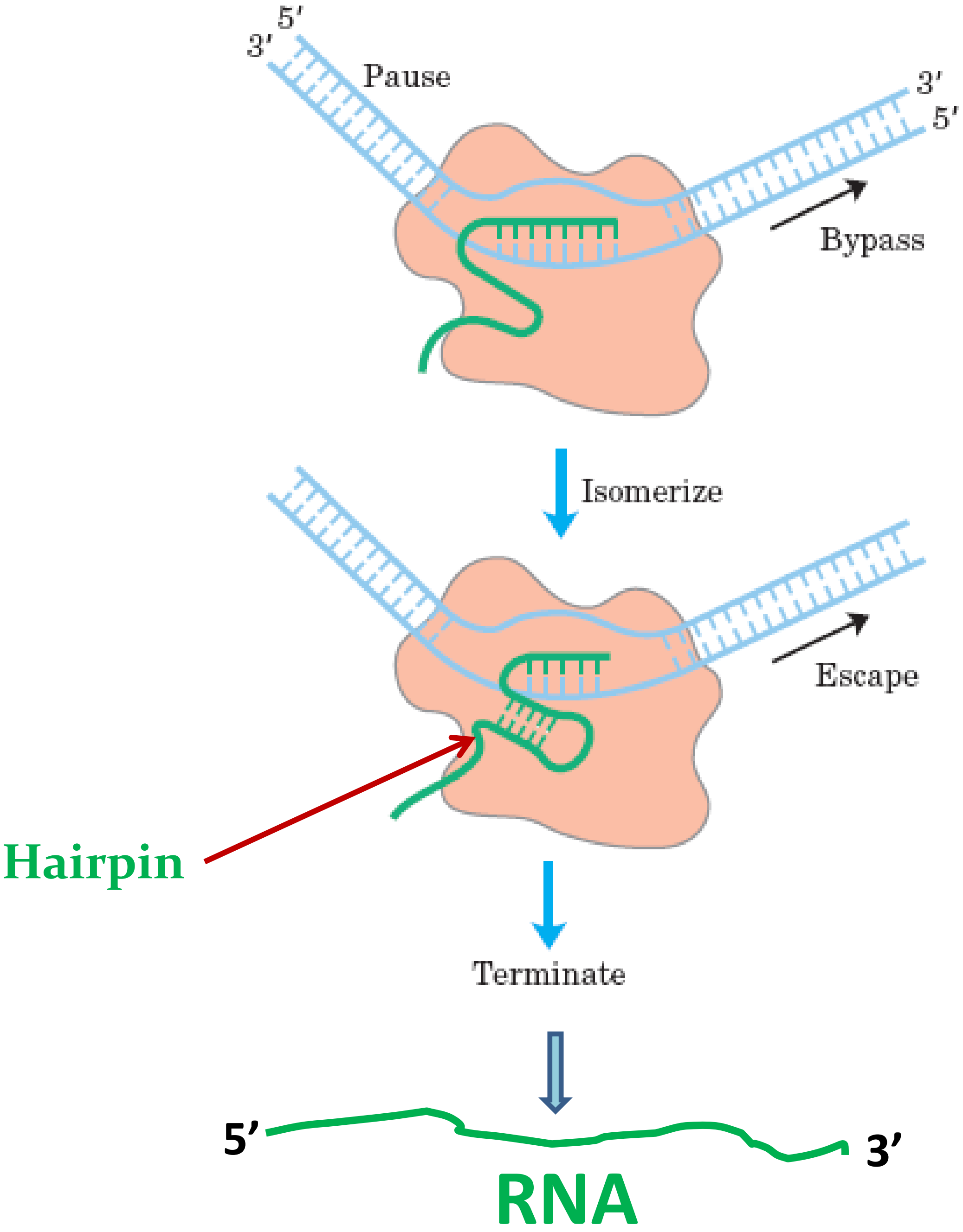
Terminazione mediate da fattore ρ (ρ-dependente)



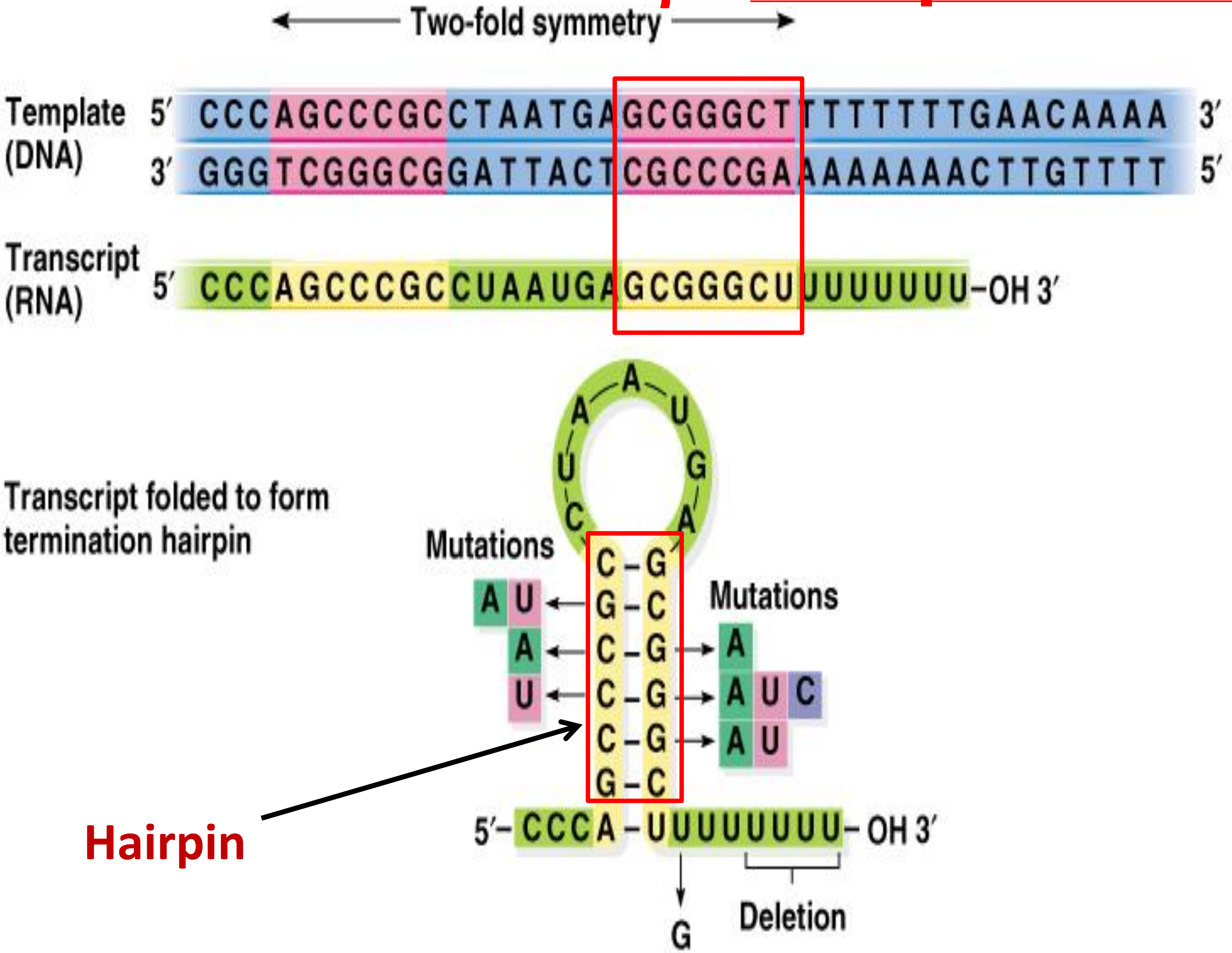
Il fattore ρ, un esamero, e’ una ATPasi e un’elicasi.

Terminazione ρ-independente

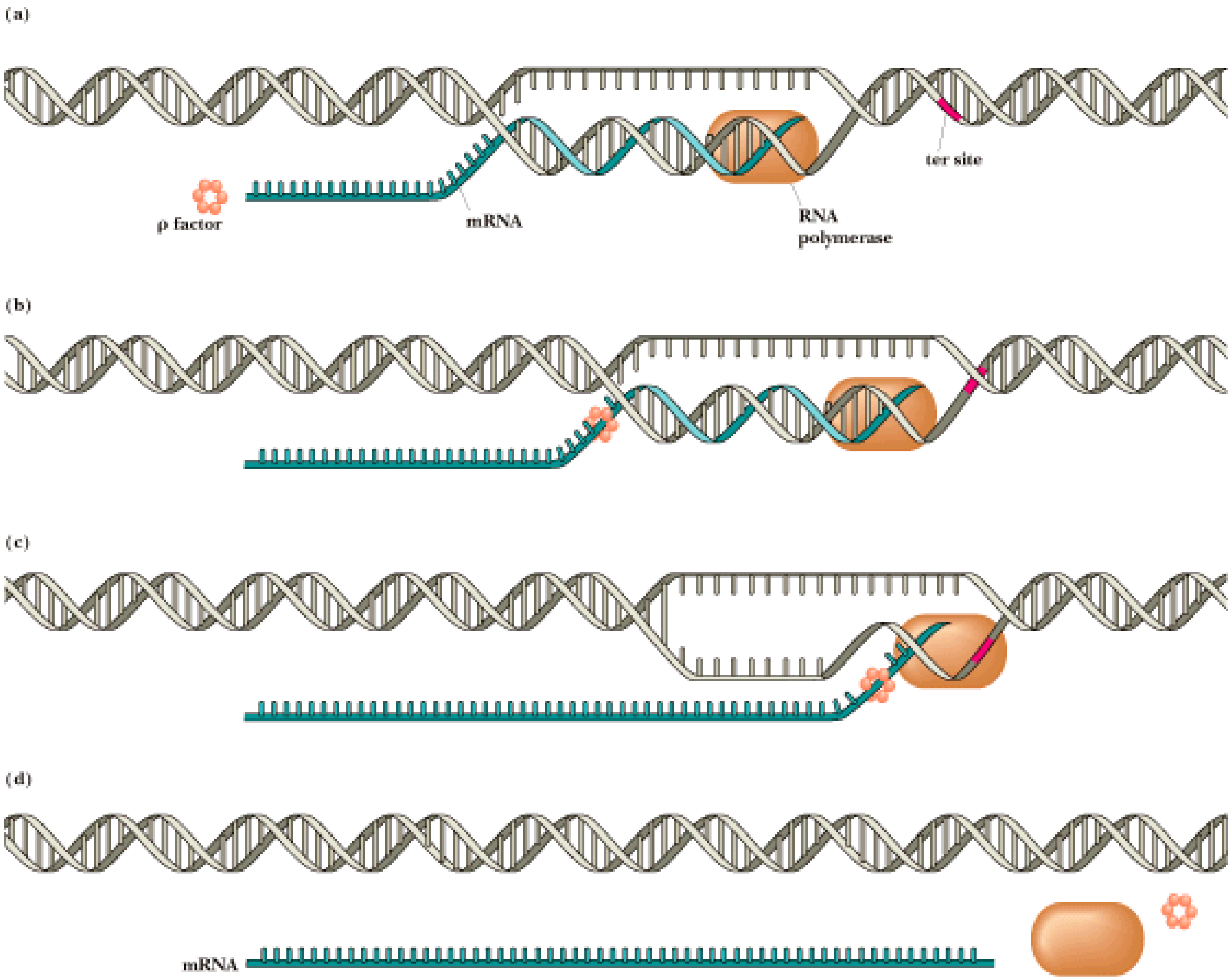
- Il segnale di terminazione e’ una sequenza di 30-40 nucleotidi sul trascritto di RNA, che consiste di molte GC seguite da una serie di U.
- La specificita’ della sequenza di questo RNA nascente fa si che si formino delle strutture stem-loop per terminare la transcrizione.


5′
3′
Pause
3′
5′
Bypass
Isomerize
Escape
Hairpin
Terminate
5′
3′
RNA

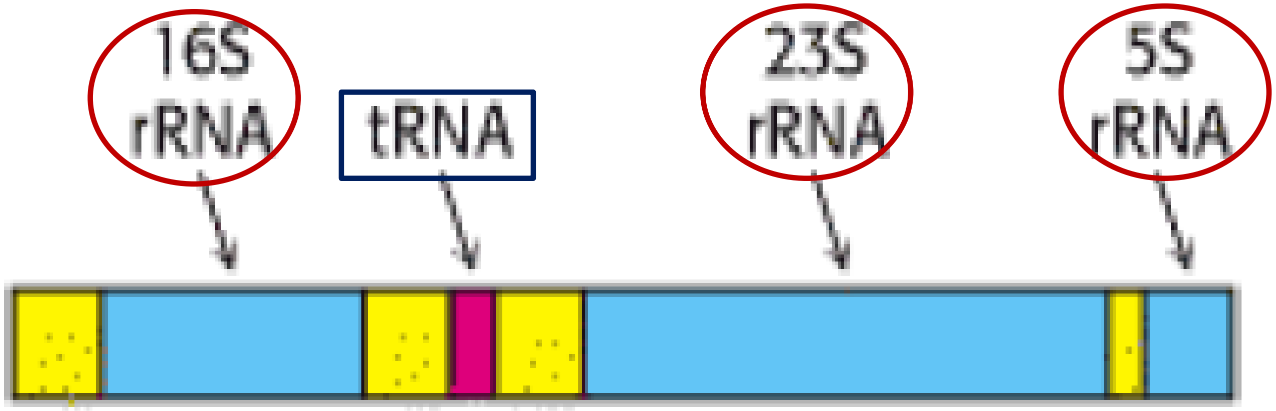
Terminazione ρ -independente



Hairpin

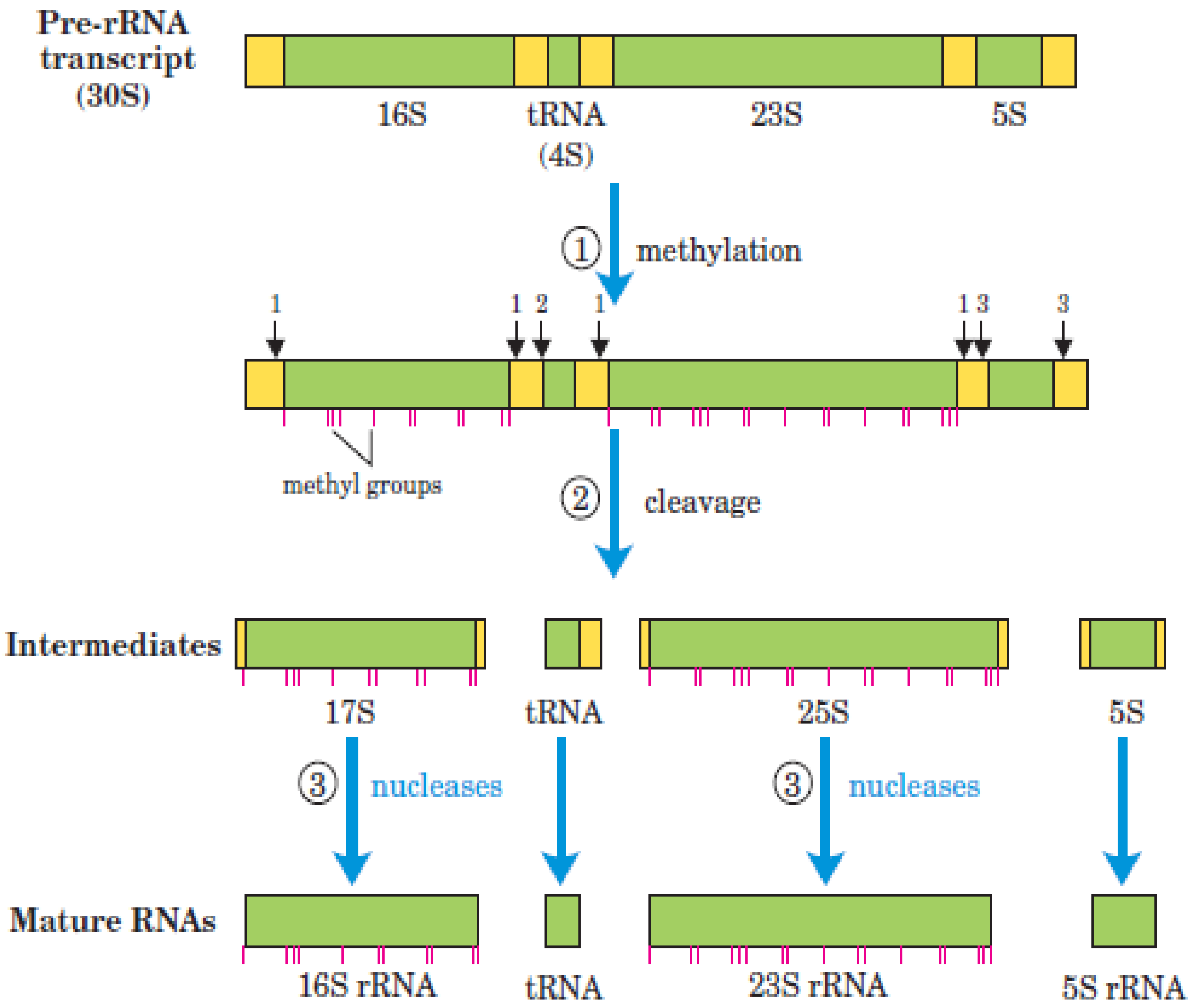

(a)
ter site
ρ factor
mRNA
RNA polymerase
(b)
(c)
(d)
mRNA

Sintesi dell' rRNA e dei tRNA

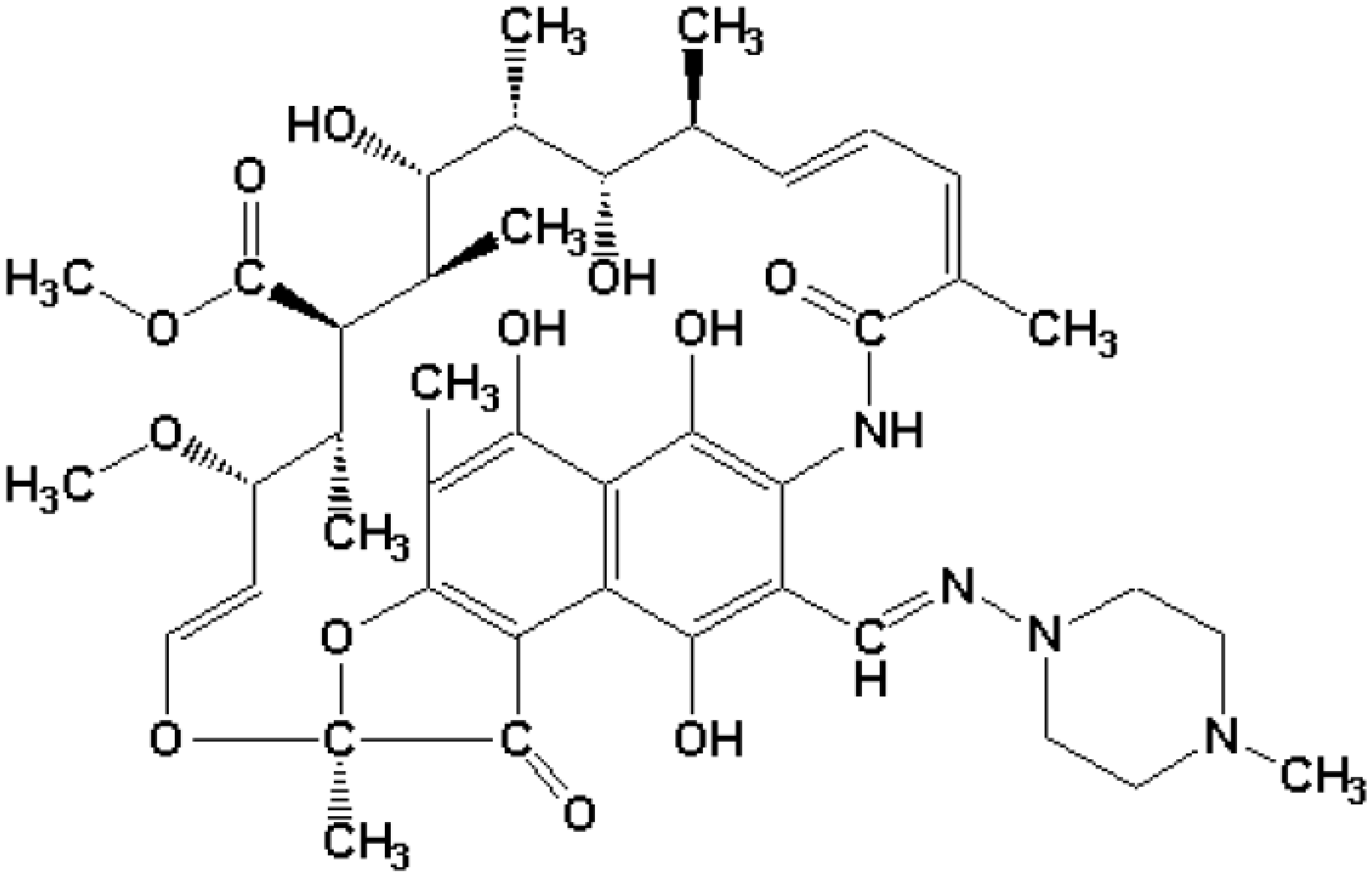


Cleavage di un trascritto policistronico produce molecule di 5S, 16S, e 23S rRNA e un tRNA molecule.

Delle regioni "Spacer" sono mostrate in giallo.

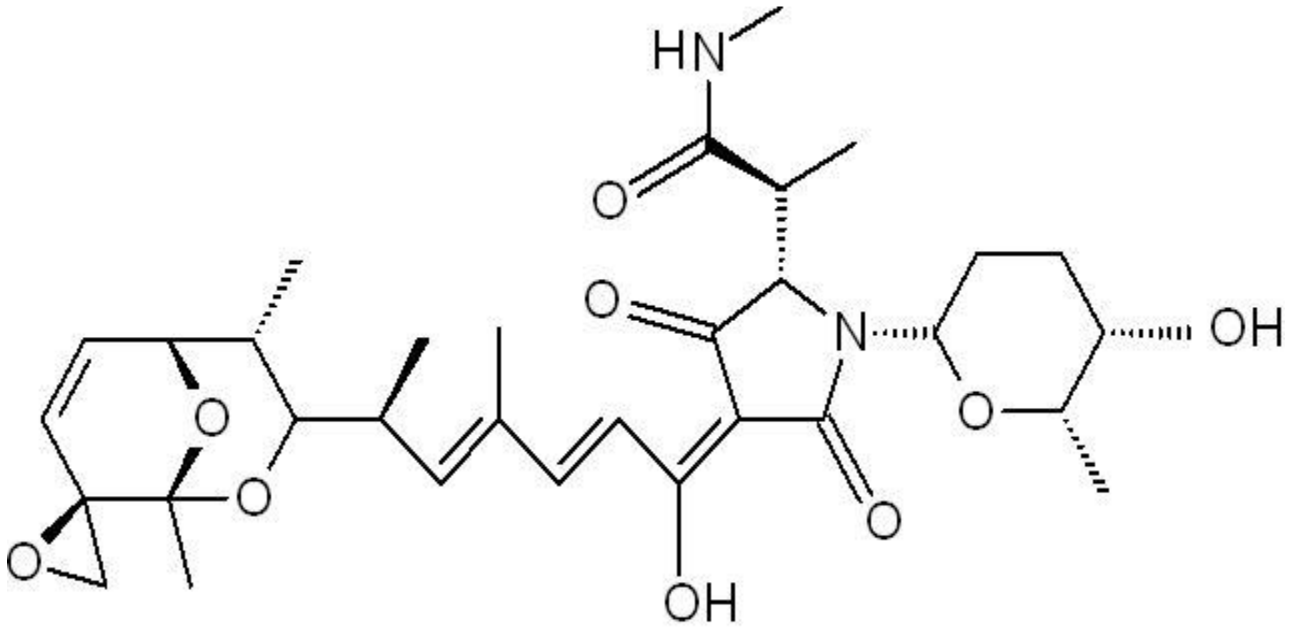

Pre-rRNA transcript (30S)
16S
tRNA (4S)
23S
5S
① methylation
1
1
2
1
1
3
3
methyl groups
② cleavage
Intermediates
17S
tRNA
25S
5S
③ nucleases
③ nucleases
Mature RNAs
16S rRNA
tRNA
23S rRNA
5S rRNA

Inibitori della trascrizione



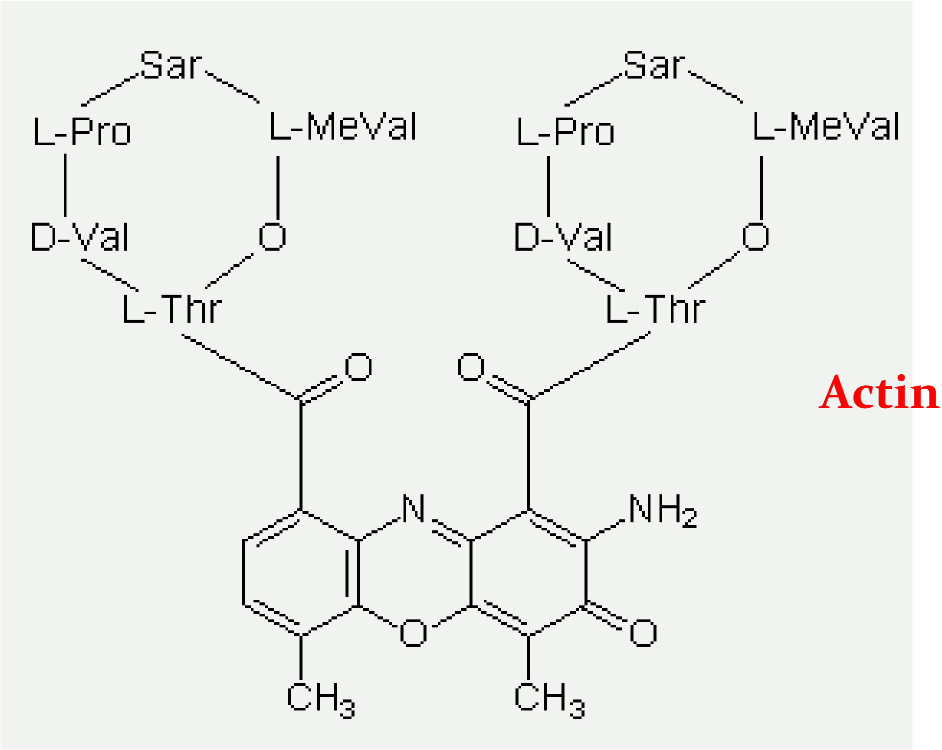
Rifampicin

Lega la subunita’ β della RNA Polymerasi e blocca l’ inizio della trascrizione.



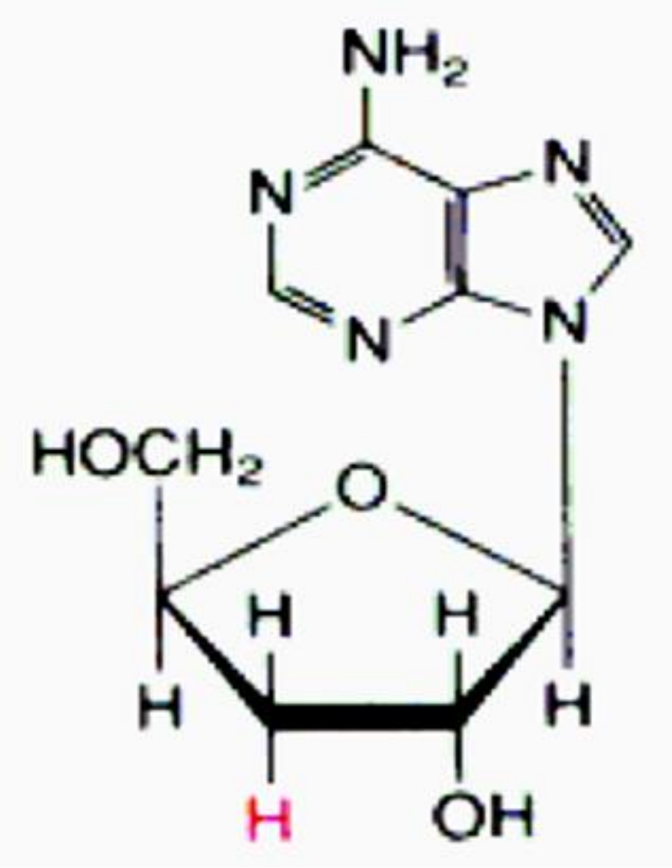
STREPTOLYDIGIN

Lega la subunita’ β della RNA Polymerasi e blocca l’ elongazione della trascrizione.



Actinomicina D

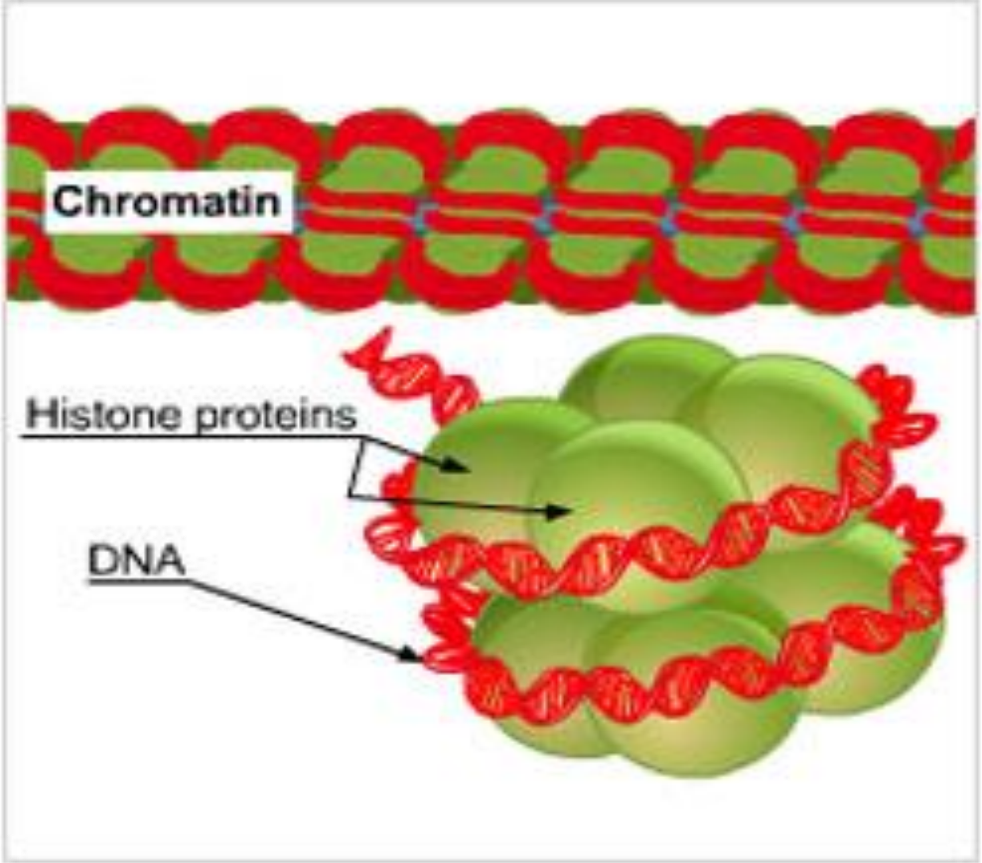
The tricyclic ring system (phenoxazone) of Actinomycin D intercalates between adjacent G-C base pairs, and the cyclic polypeptide arms fill the nearby narrow groove and inhibits Elongation phase of Transcription.

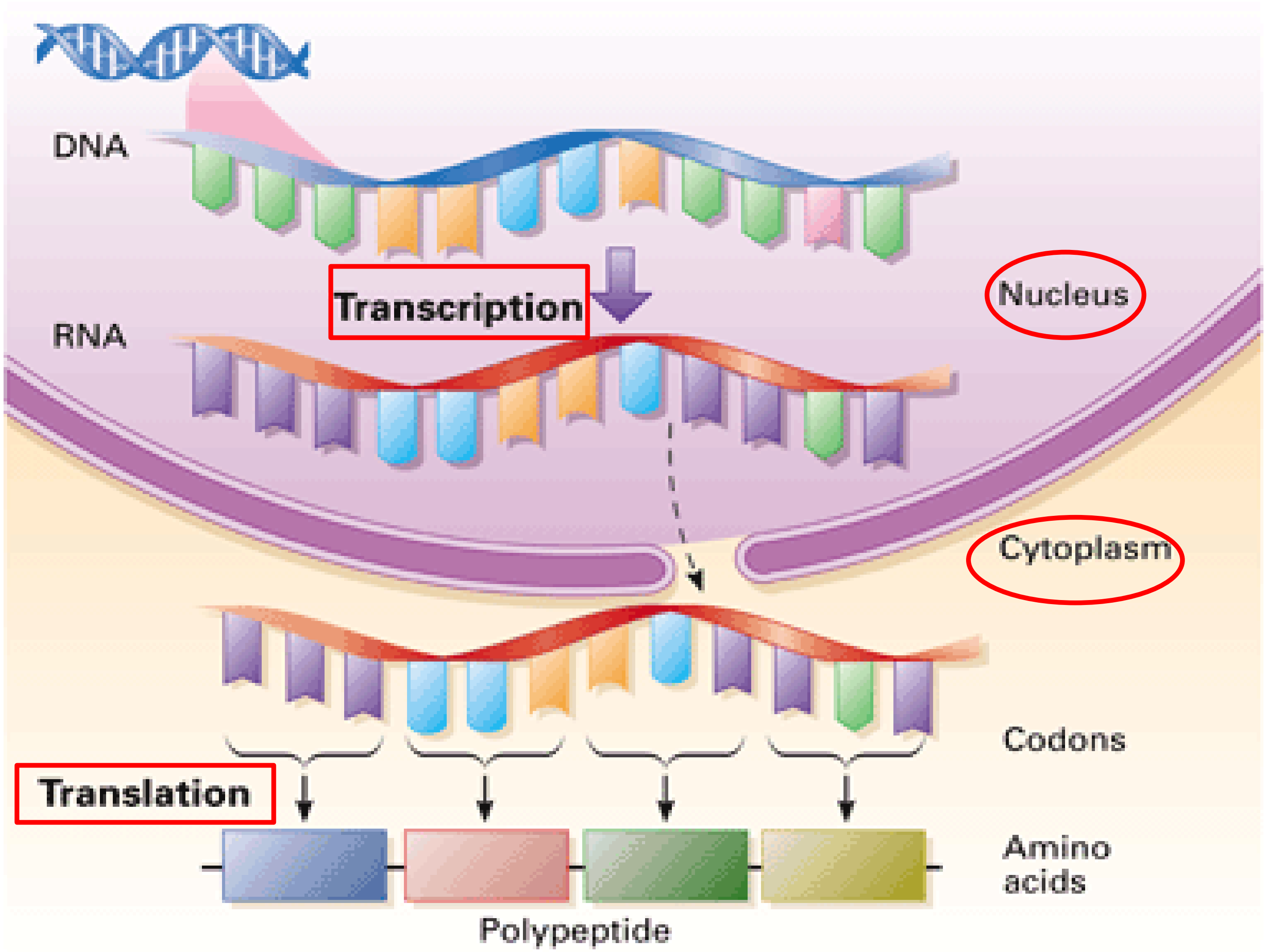


Cordycepin (3-deoxy Adenosine)

Inibisce l’ elongazione

Trascrizione eucariotica




DNA
Transcription
Nucleus
RNA
Cytoplasm
Codons
Translation
Amino acids
Polypeptide

Eukaryotic RNA polymerases

RNA Polymerase-I: Transcribes / Synthesizes

- 28s rRNA
- 18s rRNA
- 5.8s rRNA

RNA Polymerase-II: Transcribes

- m-RNA
- Some sn-RNA

RNA Polymerase-III: Transcribes

- t-RNA
- 5s rRNA
- Some sn-RNA

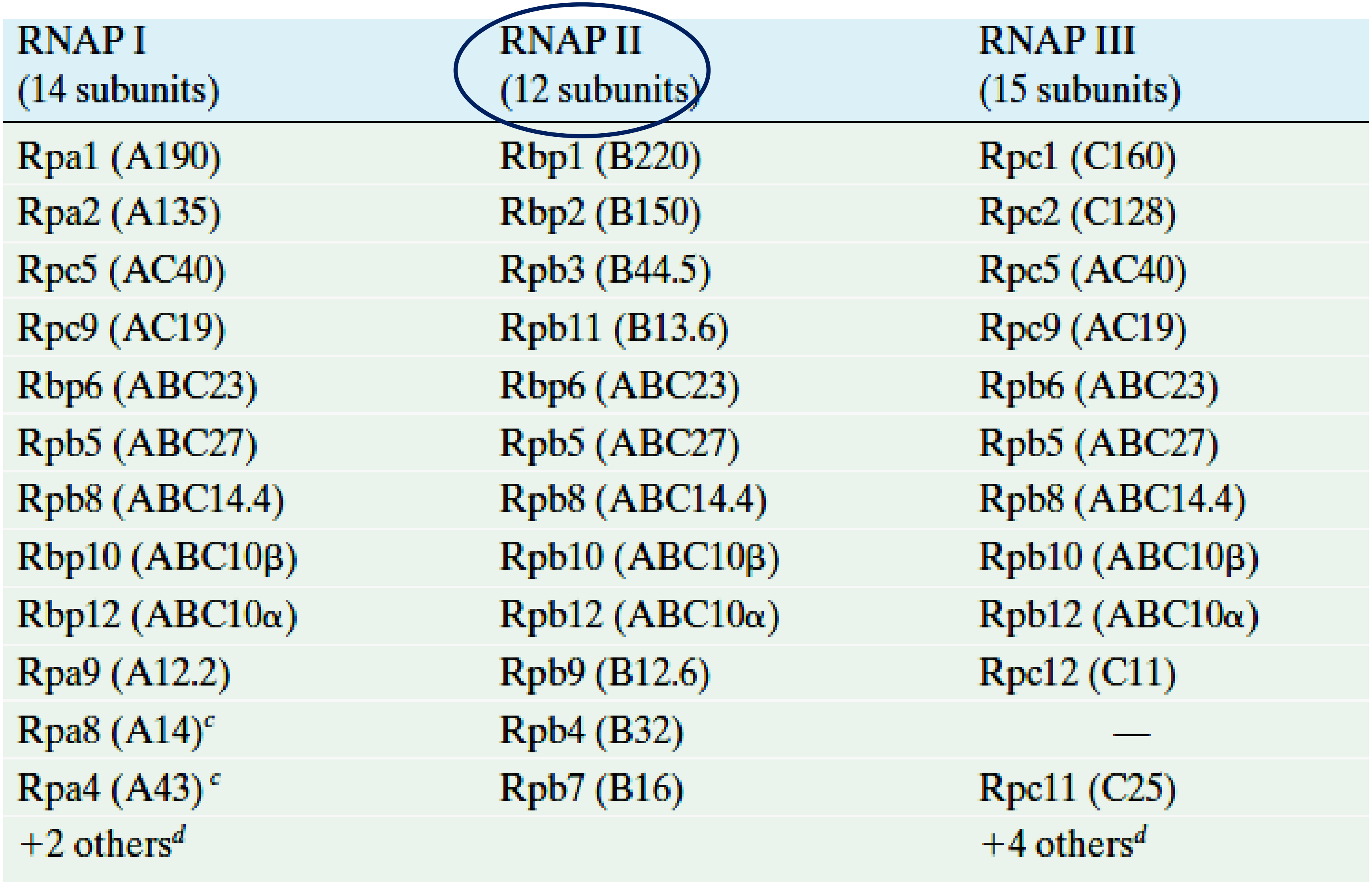
RNA POLYMERASE-II

- **RNA polymerase II** **is central to eukaryotic gene expression and has been studied extensively.**

- **RNA polymerase II** **is a multi subunit enzyme with 12 subunits.**

- **RNA polymerase II** **requires an array of other proteins, called transcription factors (TF II) in order to form the active transcription complex.**

Eukaryotic RNA polymerases



RNAP I (14 subunits)	RNAP II (12 subunits)	RNAP III (15 subunits)
Rpa1 (A190)	Rbp1 (B220)	Rpc1 (C160)
Rpa2 (A135)	Rbp2 (B150)	Rpc2 (C128)
Rpc5 (AC40)	Rpb3 (B44.5)	Rpc5 (AC40)
Rpc9 (AC19)	Rpb11 (B13.6)	Rpc9 (AC19)
Rbp6 (ABC23)	Rbp6 (ABC23)	Rpb6 (ABC23)
Rpb5 (ABC27)	Rpb5 (ABC27)	Rpb5 (ABC27)
Rpb8 (ABC14.4)	Rpb8 (ABC14.4)	Rpb8 (ABC14.4)
Rbp10 (ABC10β)	Rpb10 (ABC10β)	Rpb10 (ABC10β)
Rbp12 (ABC10α)	Rpb12 (ABC10α)	Rpb12 (ABC10α)
Rpa9 (A12.2)	Rpb9 (B12.6)	Rpc12 (C11)
Rpa8 (A14)[c]	Rpb4 (B32)	—
Rpa4 (A43)[c]	Rpb7 (B16)	Rpc11 (C25)
+2 others[d]		+4 others[d]

α-Amanitin (Fungal toxin from *Amanita phalloides*) - cyclic octapeptide with unussual amino acids.

Chapter 13 Opener
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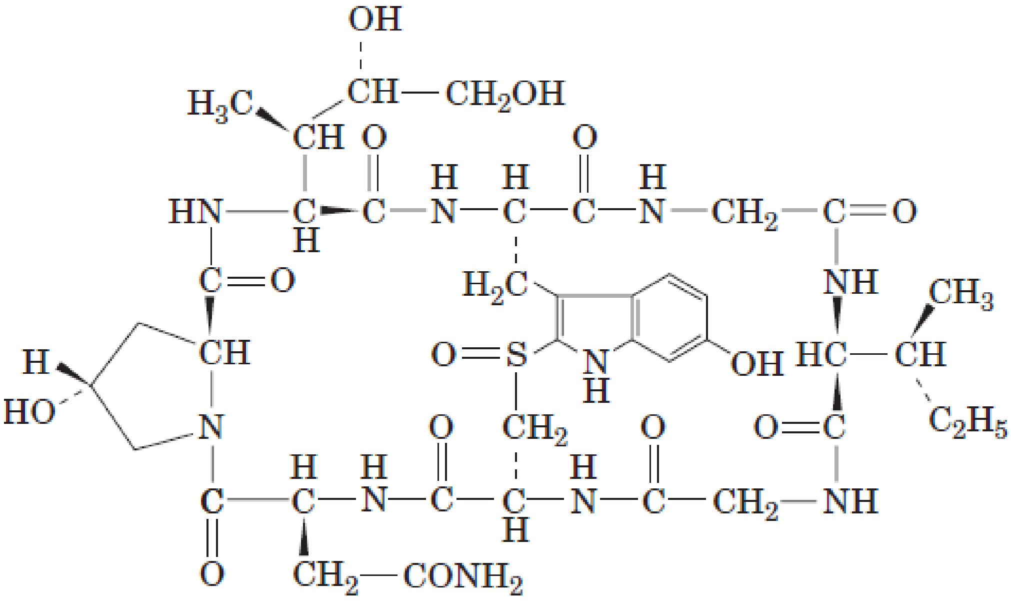


α-Amanitin

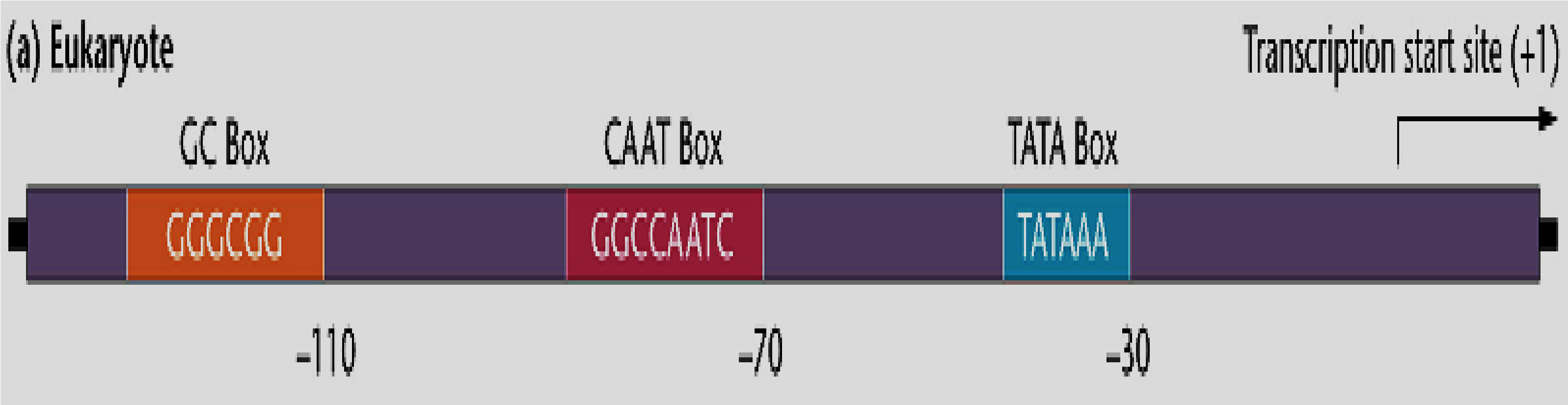
Inhibitor of eukaryotic RNA polymerase (mainly of type II)

Type	Location	Cellular transcripts	Effects of α-amanitin
I	Nucleolus	18S, 5.8S, and 28S rRNA	Insensitive
II	Nucleoplasm	mRNA precursors and snRNA	Strongly inhibited
III	Nucleoplasm	tRNA and 5S rRNA	Inhibited by high concentrations

Eukaryotic Transcription

Promoters

- ✓ Much more complex than those found in bacteria.
- ✓ These are consensus sequences located at the upstream regions of Coding strand.
- ✓ Mutation of this region usually significantly lowers the rate of transcription.



1) TATA box (Hogness Box)

Very similar to the prokaryotic TATA box, except the sequence is slightly different (TATAAA) and it is located in between -25 to -30.

2) CAAT box

Located in between -70 to -80.

Always contains CCAAT.

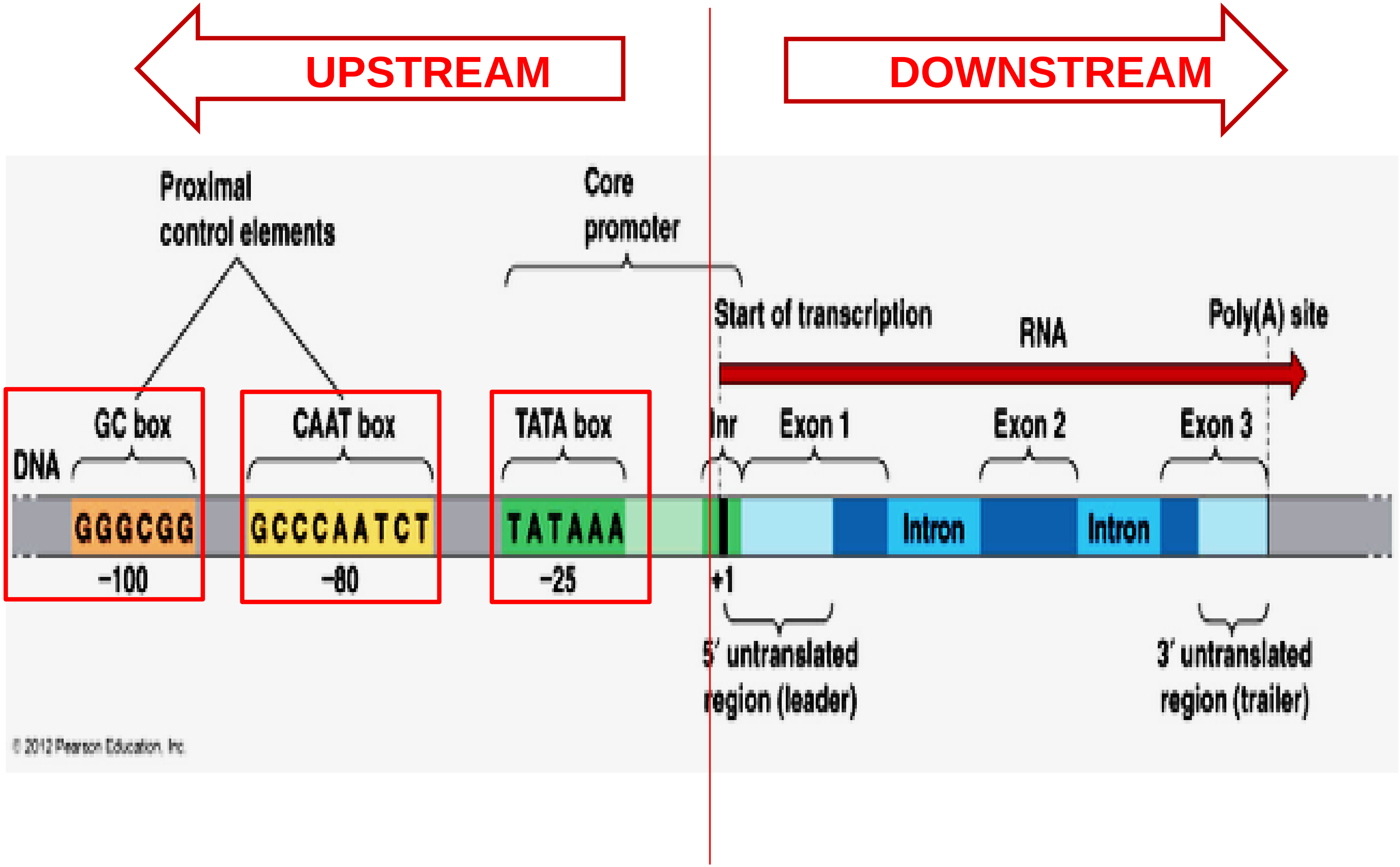
3) GC box

Usually has the sequence GGGCGG and is typically found at -110.

ENHANCERS :

- Enhancers elements are the sequences located in a variety of regions of a gene both upstream and downstream of the transcription start site and even within the transcribed portions of some genes.

- Enhancers increases the transcription rate by several folds.



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Transcription factors

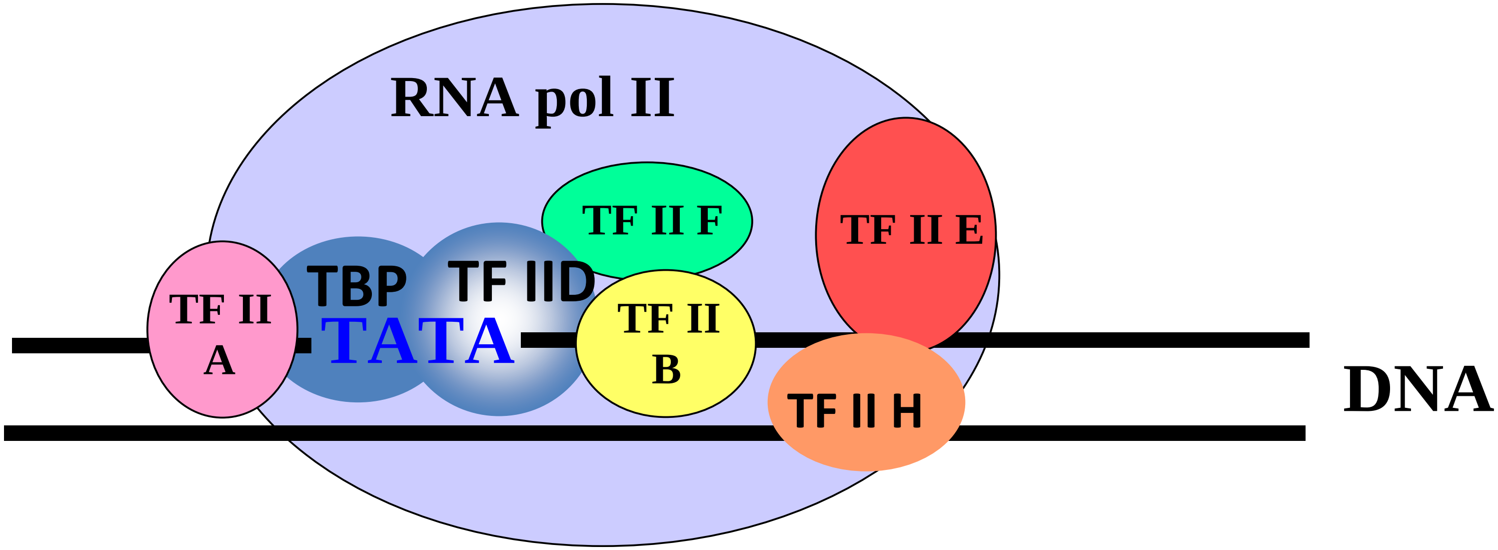
- **RNA-pol II does not bind to the promoter sequences directly.**
- **RNA-pol II associates with six transcription factors.**
- **TFII A, TFII B, TFII D, TFII E, TFII F and TFII H**

Proteins Required for Initiation of Transcription at the RNA Polymerase II (Pol II)

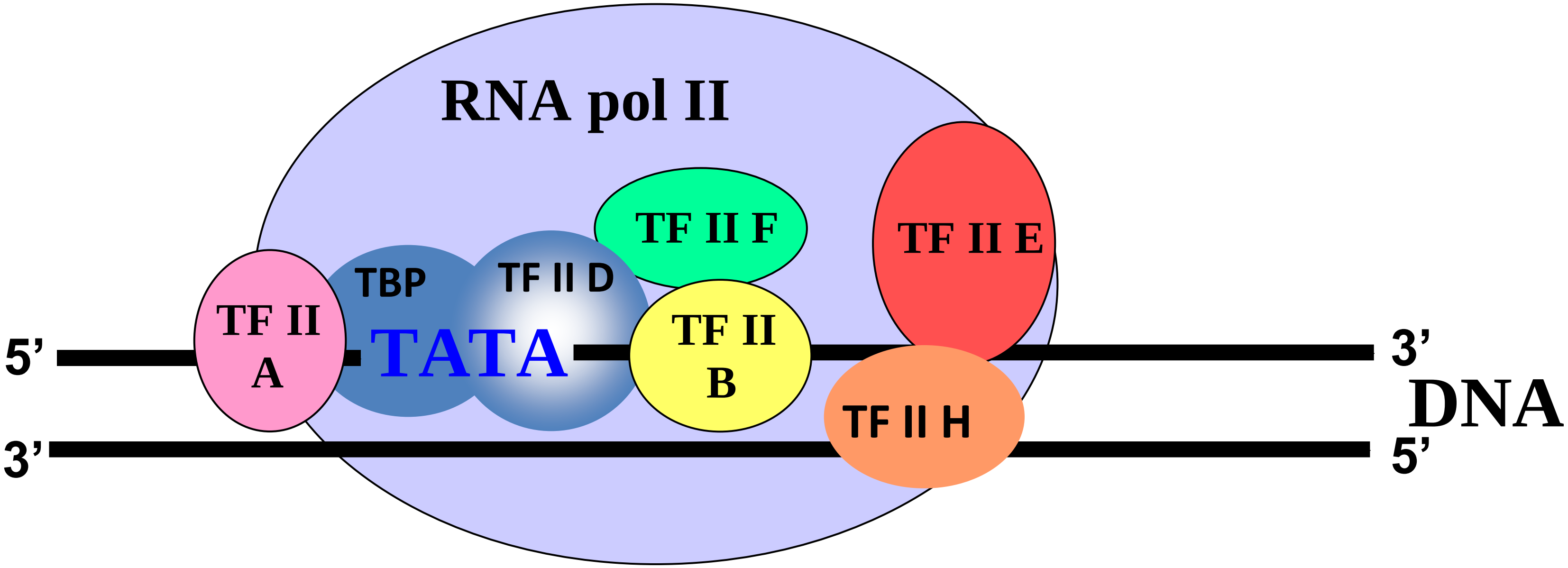
Transcription protein	*Number of subunits*	*Subunit(s) M_r*	*Function(s)*
Initiation			
Pol II	12	10,000–220,000	Catalyzes RNA synthesis
TBP (TATA-binding protein)	1	38,000	Specifically recognizes the TATA box
TFIIA	3	12,000, 19,000, 35,000	Stabilizes binding of TFIIB and TBP to the promoter
TFIIB	1	35,000	Binds to TBP; recruits Pol II–TFIIF complex
TFIIE	2	34,000, 57,000	Recruits TFIIH; has ATPase and helicase activities
TFIIF	2	30,000, 74,000	Binds tightly to Pol II; binds to TFIIB and prevents binding of Pol II to nonspecific DNA sequences
TFIIH	12	35,000–89,000	Unwinds DNA at promoter (helicase activity); phosphorylates Pol II (within the CTD); recruits nucleotide-excision repair proteins
Elongation[*]			
ELL[†]	1	80,000	
p-TEFb	2	43,000, 124,000	Phosphorylates Pol II (within the CTD)
SII (TFIIS)	1	38,000	
Elongin (SIII)	3	15,000, 18,000, 110,000	

Pre-initiation complex (PIC)

- **TBP of TFII D binds TATA–Box(-10 sequence)**
- **TFII A and TFII B bind TFII D**
- **TFII F- RNA-pol complex binds TFII B**
- **TFII F and TFII E open the dsDNA (helicase and ATPase)**
- **TFII H: completion of PIC**



Pre-initiation complex (PIC)



DNA + RNA Poly-II + TBP + Transcription Factors (TF)

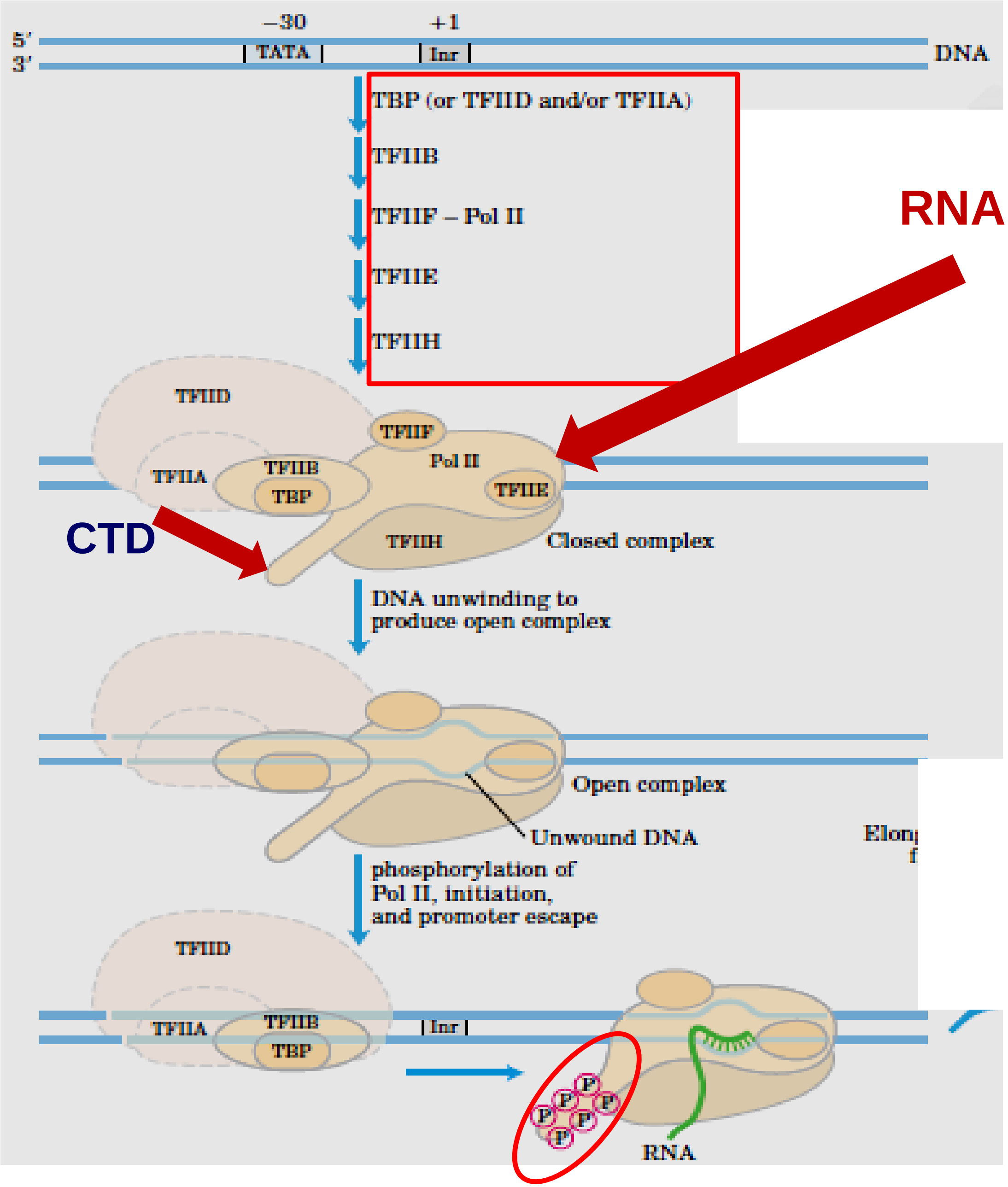
Phosphorylation of RNA-Polymerase-II

- TF II H is of protein kinase activity to phosphorylate CTD of RNA pol-II.

(CTD is the C-terminal domain of RNA pol-II)

- Only the RNA Polymerase can move downstream, starting the elongation phase.

- Most of the Transcription Factors fall off from PIC during the elongation phase.



RNA Poly-II

CTD

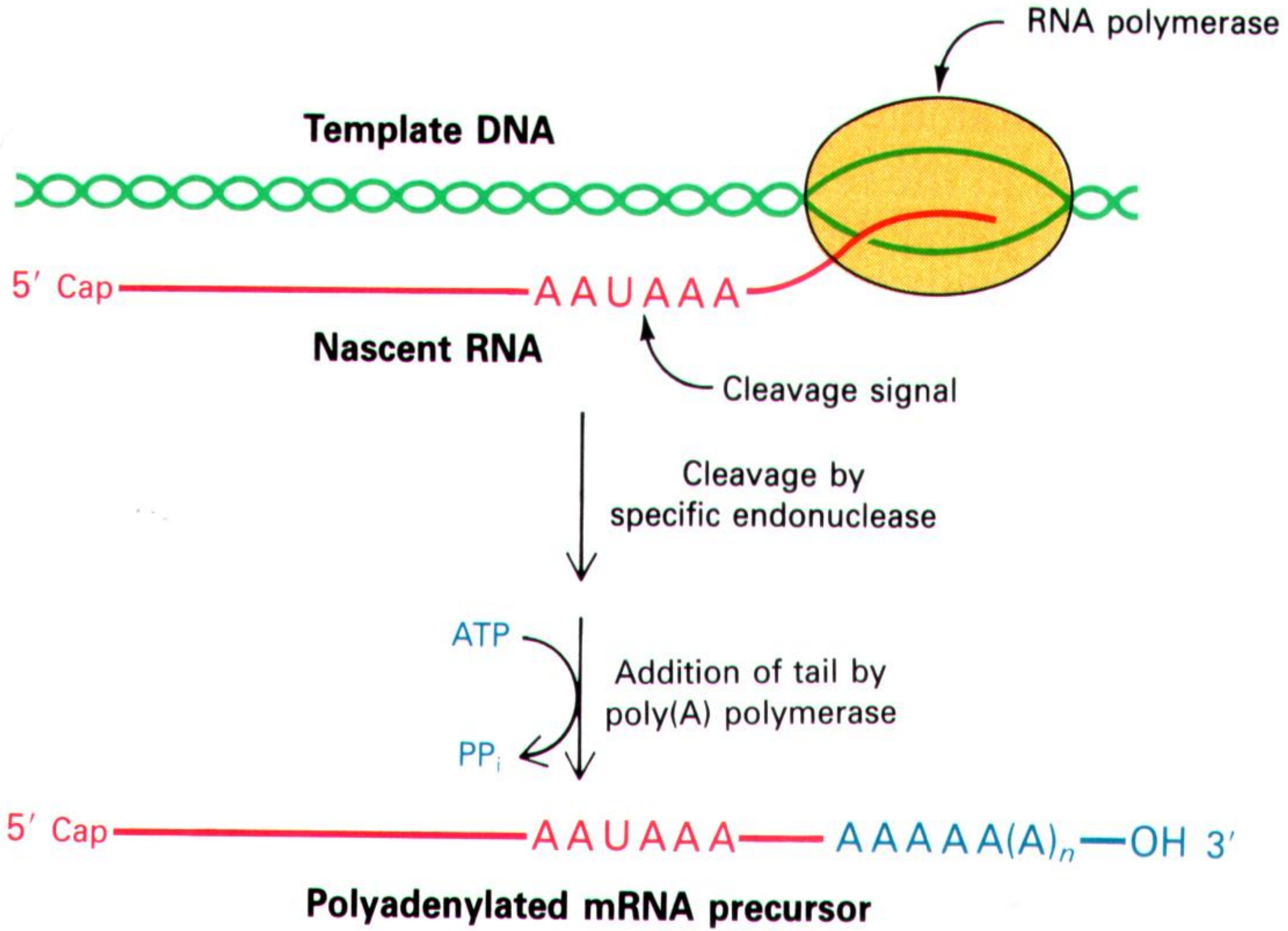
Termination

- **When the RNA Polymerase transcribes the terminator region of the DNA, the polymerase releases the mRNA**
- **The termination sequence is AATAAA followed by GT repeats.**

Elongation

TFIIF remains associated with RNA Pol-II throughout elongation.

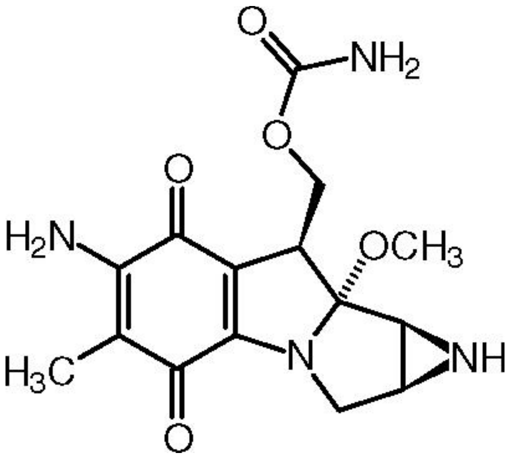
The activity of the RNA poly-II is greatly enhanced by proteins called Elongation factors


RNA polymerase
Template DNA
5′ Cap
AAUAAA
Nascent RNA
Cleavage signal
Cleavage by specific endonuclease
ATP
PP$_i$
Addition of tail by poly(A) polymerase
5′ Cap
AAUAAA
AAAAA(A)$_n$—OH 3′
Polyadenylated mRNA precursor

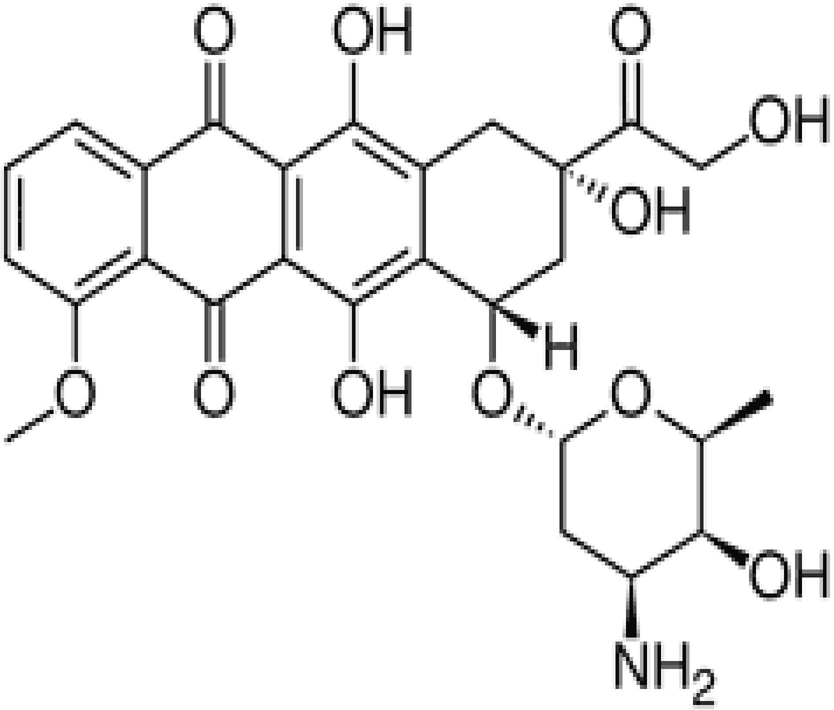
Inibitori della trascrizione eucariotica

Mitomycin

- Mitomycin- **Intercalates with DNA strands**
- Blocks transcription
- Used as **anticancer drug**

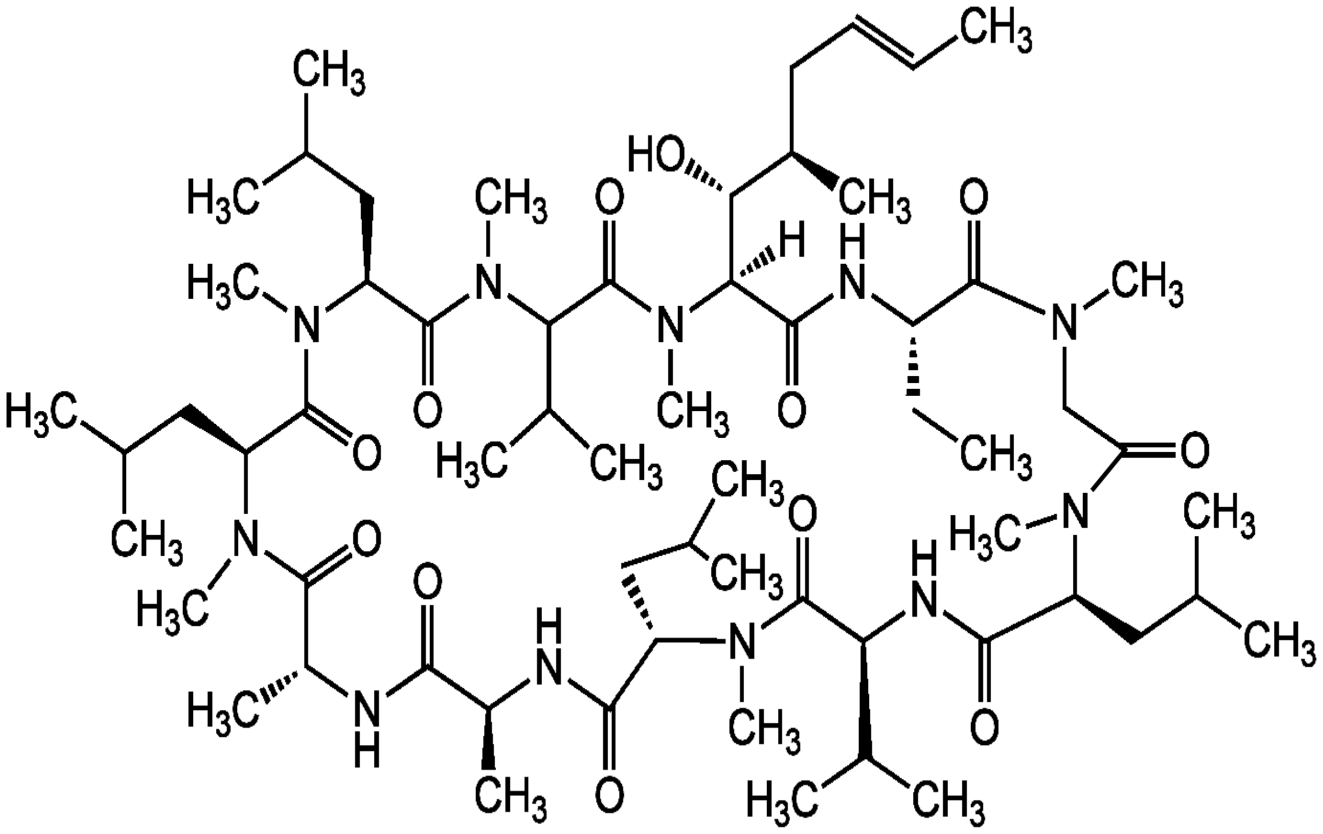


ADRIAMYCIN



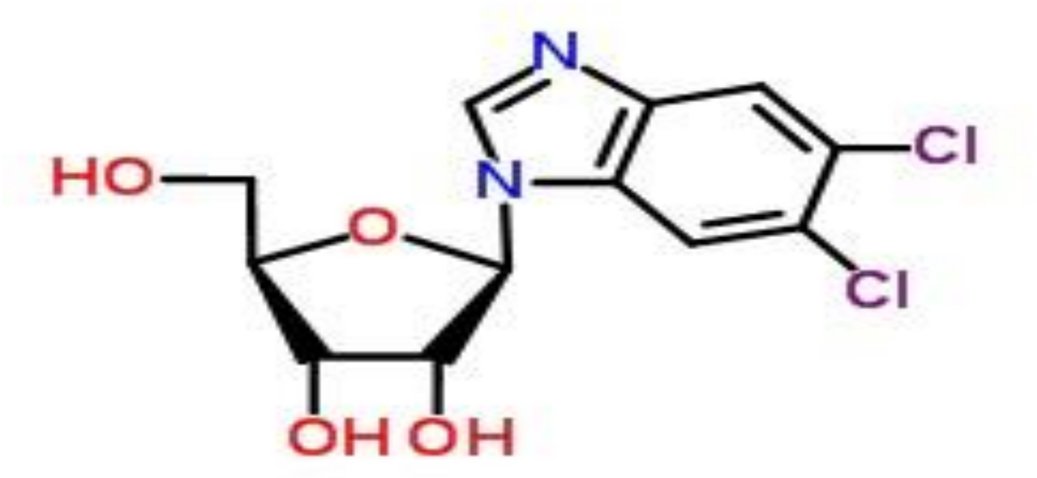
Inhibits the Initiation phase by preventing the interaction of TF-IID with RNA-Poly-II and DNA complex.

CYCLOSPORIN -A



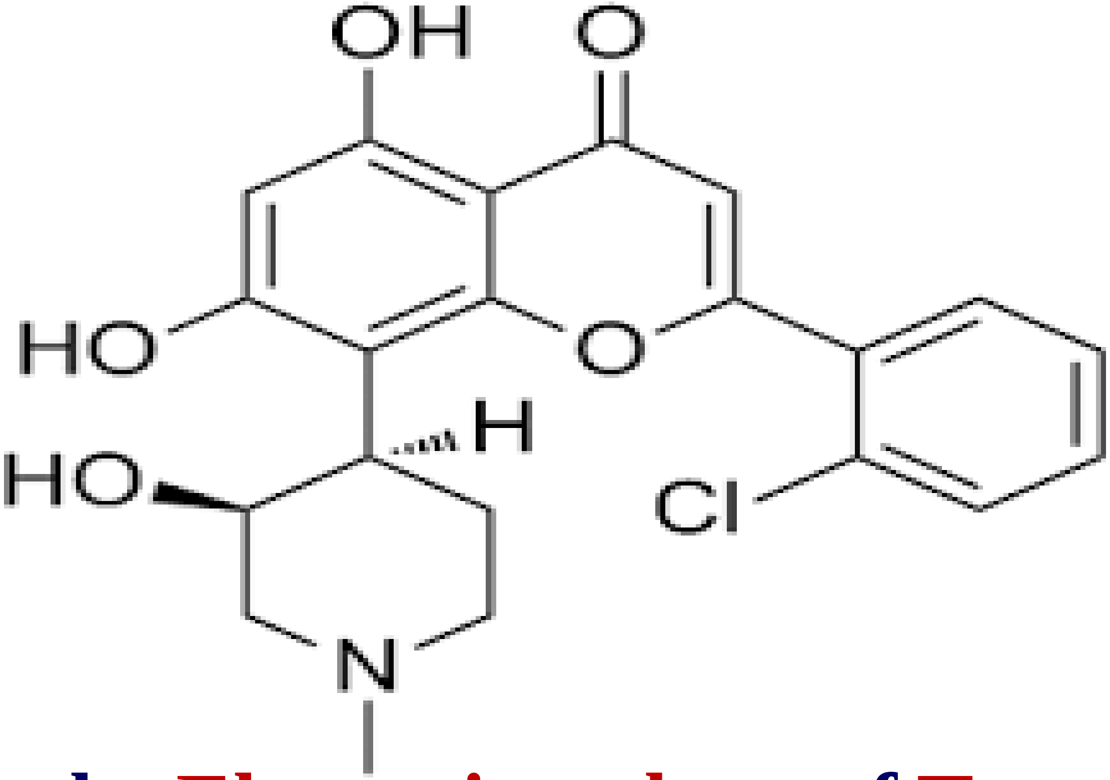
Immunosuppressant Drug inhibits Transcription in T-Cells.

DRB
(5,6-dichlorobenzimidazone-1-β-D-ribofuranoside)



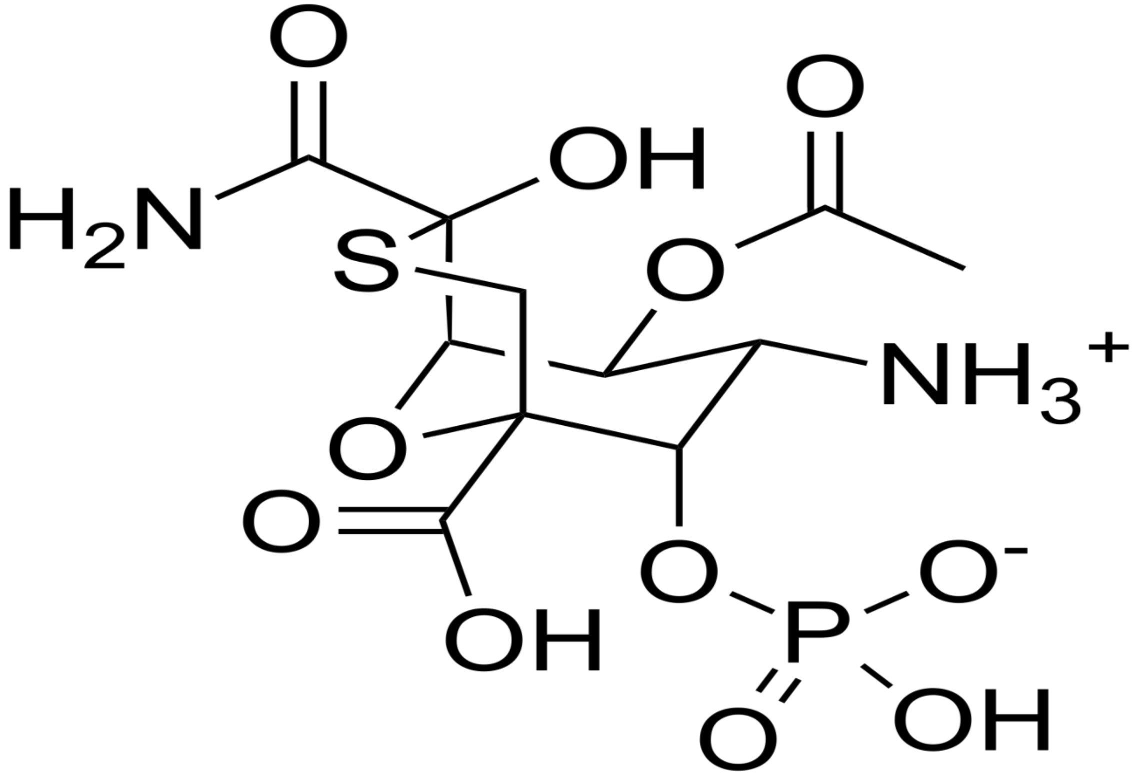
Inhibits the Elongation phase of Transcription by selectively inhibiting RNA Poly-II.

Flavopyridol (Alvocidib)



Inhibits the Elongation phase of Transcription by selectively inhibiting RNA Poly-II.

Tagetitoxin

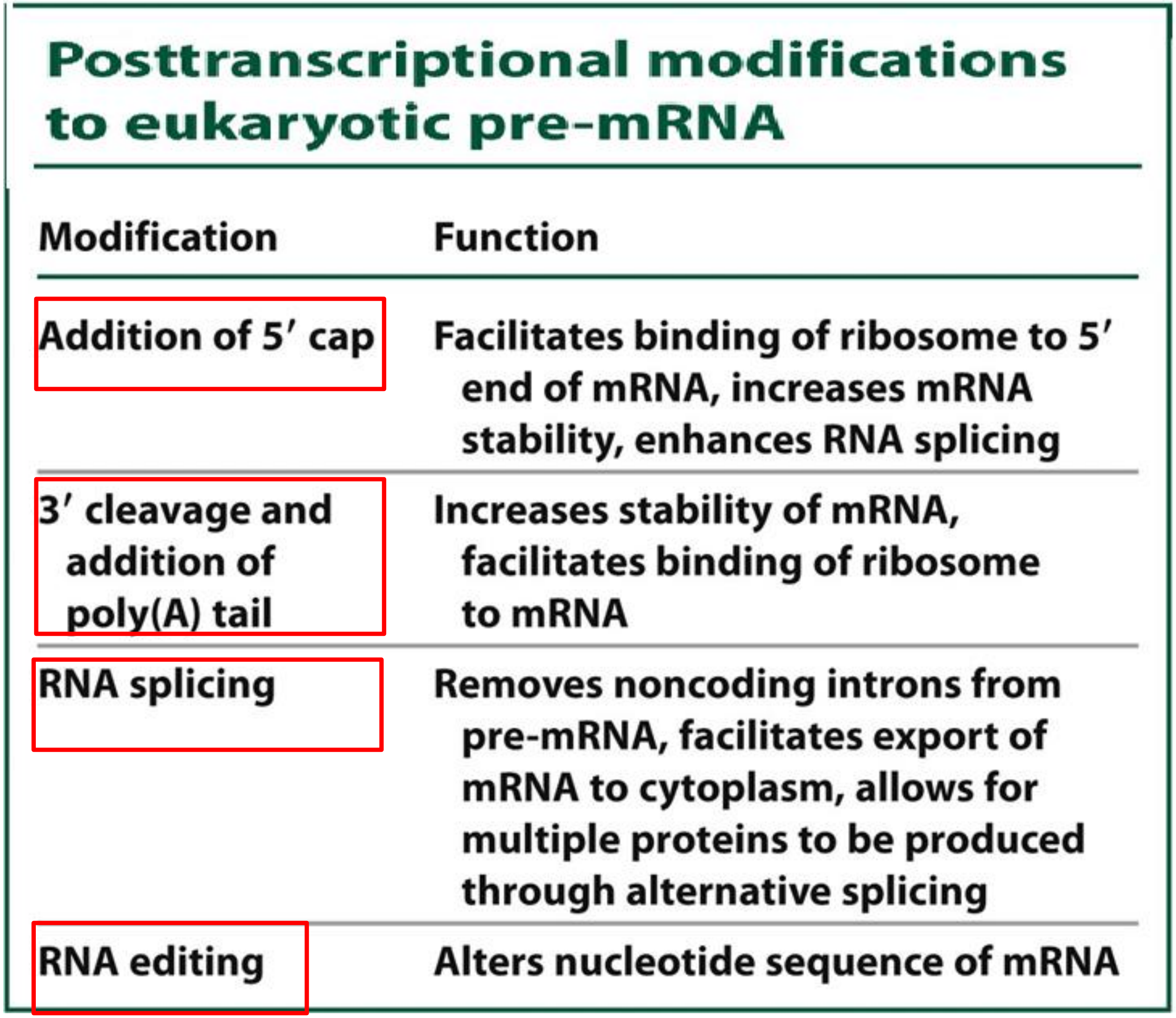


Inhibits tRNA synthesis by binding to RNA Poly-III.

Post-Transcriptional Modifications

- **The nascent RNA, also known as Primary transcript, needs to be modified to become functional, mRNAs, tRNAs and rRNAs.**

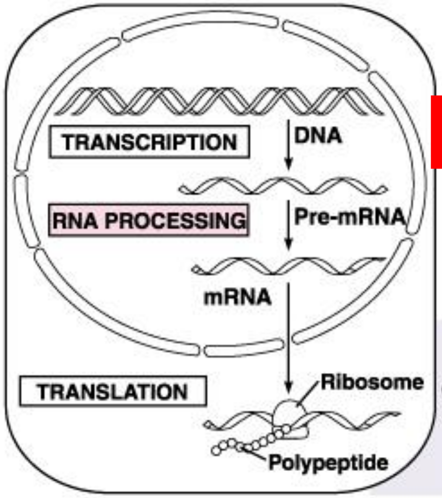
- **These modification is critical to eukaryotic systems.**

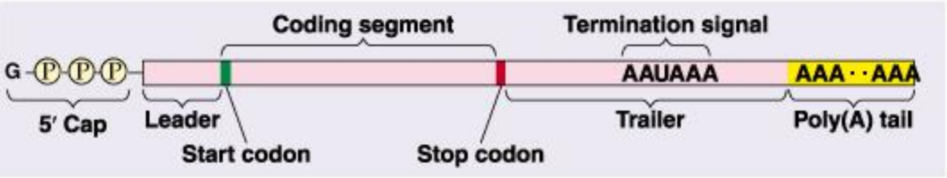


Posttranscriptional modifications to eukaryotic pre-mRNA

Modification	Function
Addition of 5′ cap	Facilitates binding of ribosome to 5′ end of mRNA, increases mRNA stability, enhances RNA splicing
3′ cleavage and addition of poly(A) tail	Increases stability of mRNA, facilitates binding of ribosome to mRNA
RNA splicing	Removes noncoding introns from pre-mRNA, facilitates export of mRNA to cytoplasm, allows for multiple proteins to be produced through alternative splicing
RNA editing	Alters nucleotide sequence of mRNA

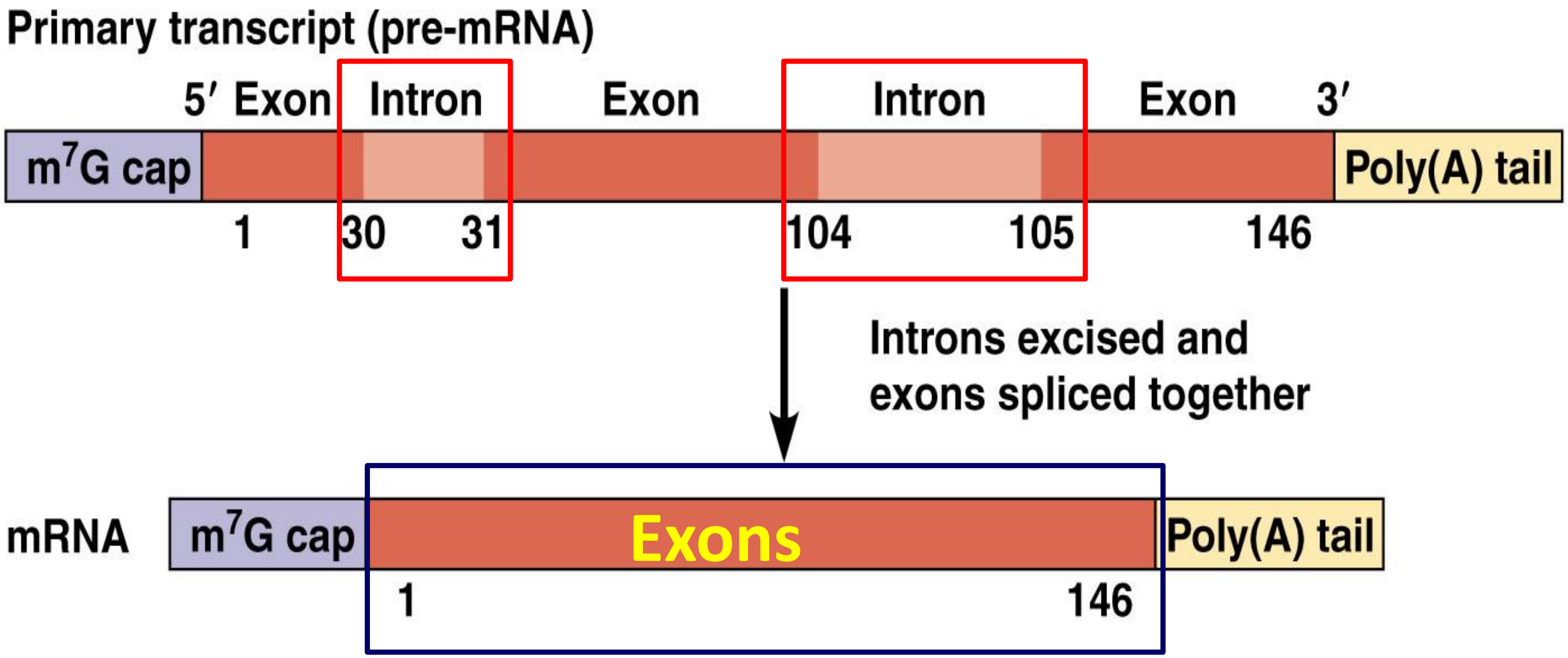
Modification of hnRNA





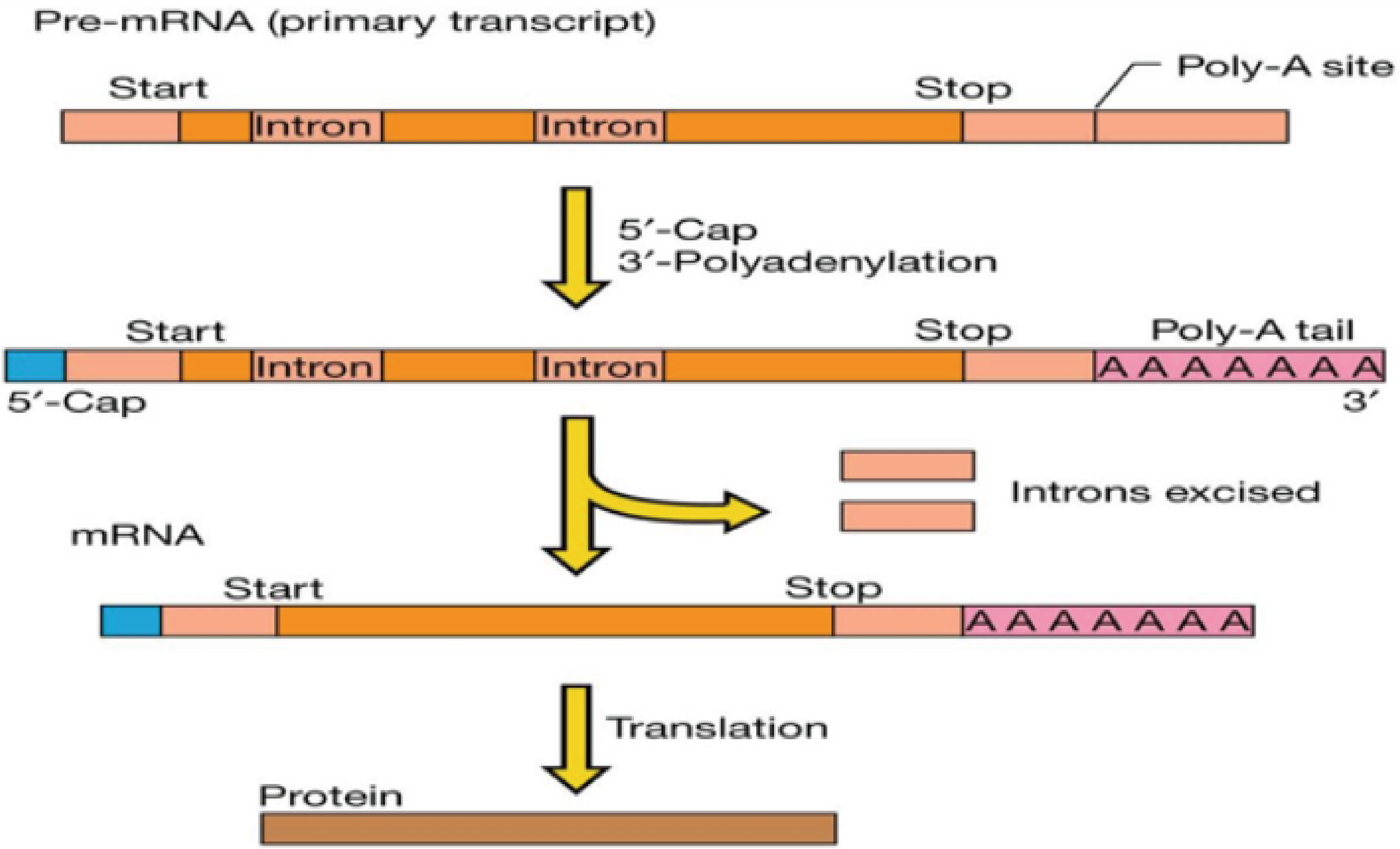
- **Primary transcripts of mRNA are called as heteronuclear RNA (hnRNA).**
- **hnRNA are larger than matured mRNA by many folds.**
- **Modification includes**
  - **Capping at the 5′- end**
  - **Tailing at the 3′- end**
  - **mRNA splicing**
  - **RNA editing**

Post Transcriptional modifications of Pre-mRNA (or) hnRNA

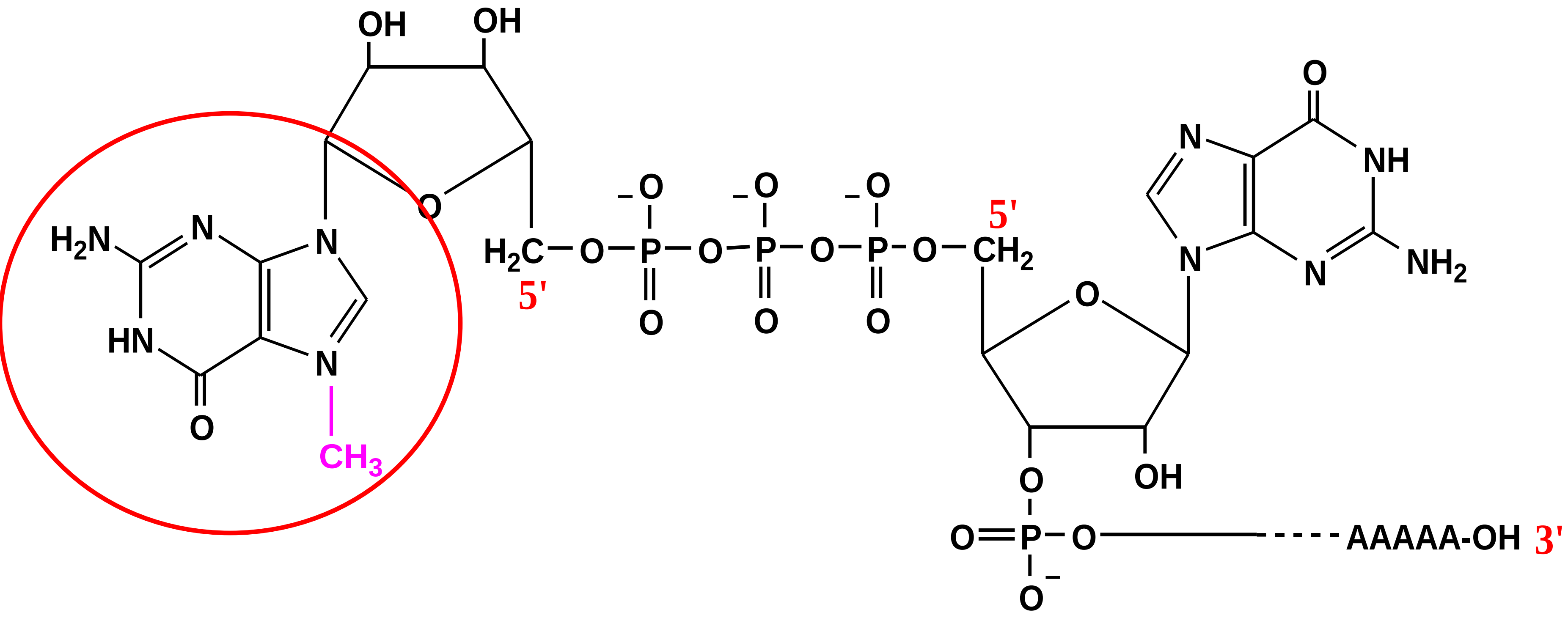


- **Introns** are removed from the primary transcript in the nucleus, **exons (coding sequences)** are ligated to form the mRNA molecule.

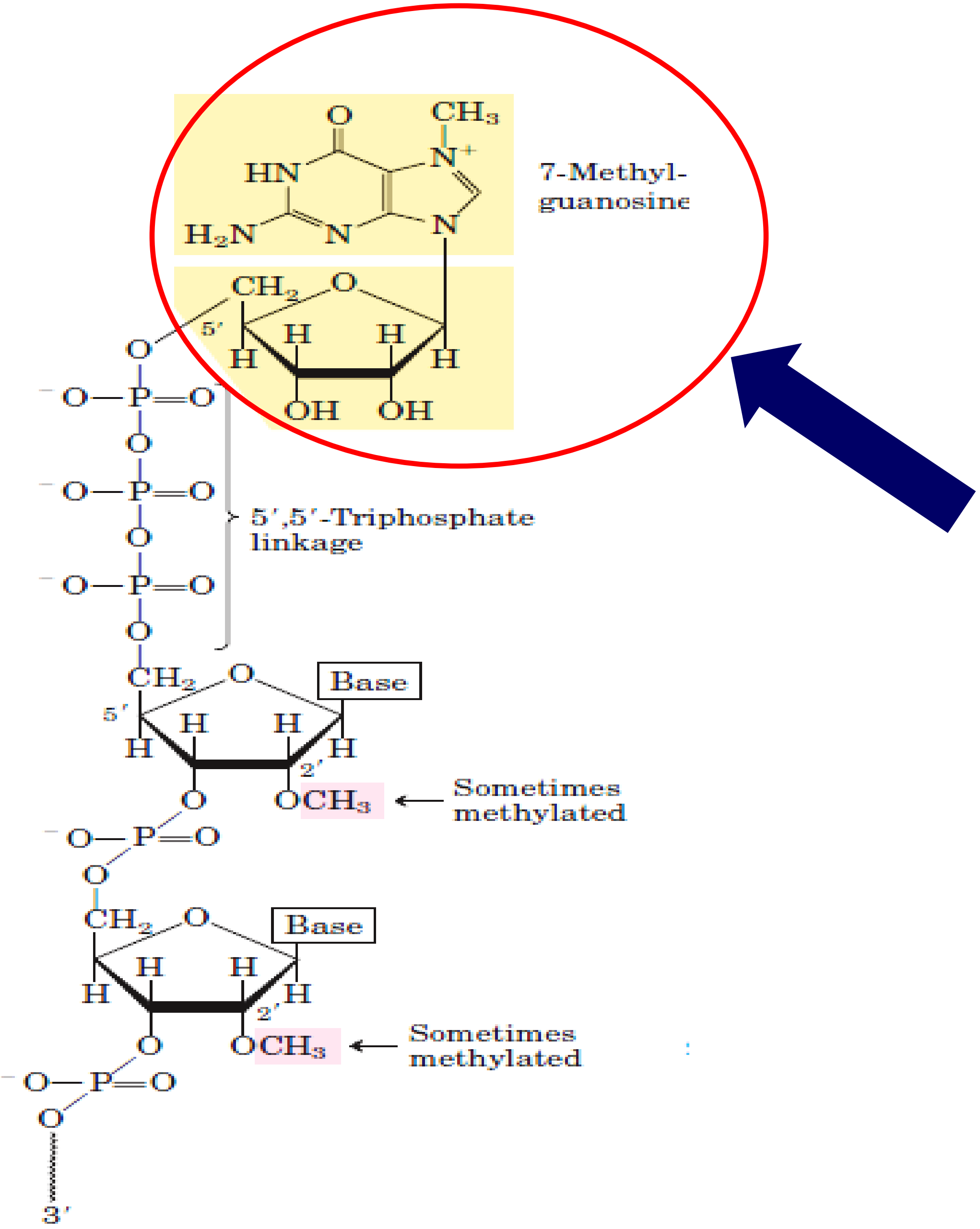
pre-mRNA maturation



Capping at the 5′- end



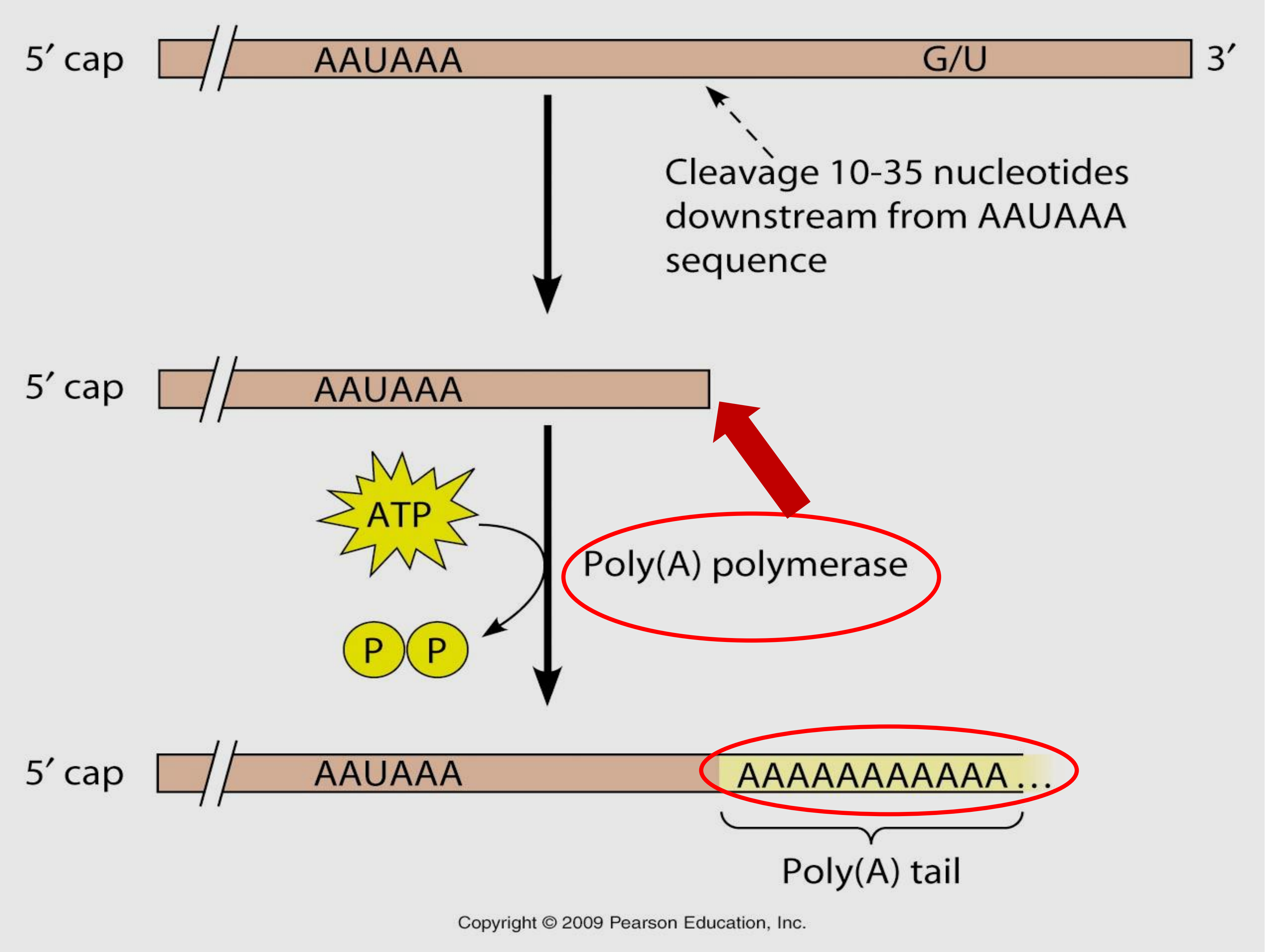
m^{7}GpppGp----

7-Methyl-guanosine
5′,5′-Triphosphate linkage
Base
Sometimes methylated
Base
Sometimes methylated
5′
2′
3′

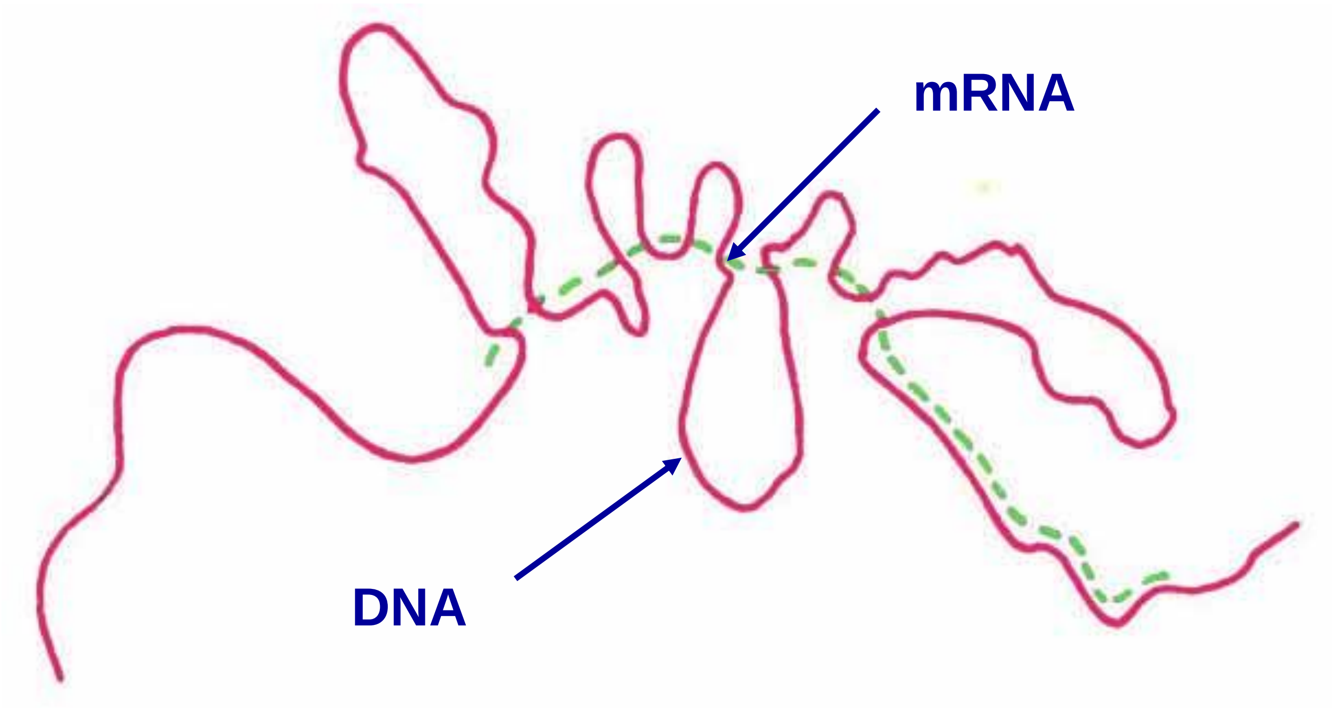
5' Cap

- The **5′- cap structure** is found on **hnRNA** too. ⇒ The capping process occurs in **nuclei**.
- The cap structure of mRNA will be recognized by the **cap-binding protein** required for translation.
- The **capping** occurs **prior to** the splicing.

Poly-A tailing at 3′ - end



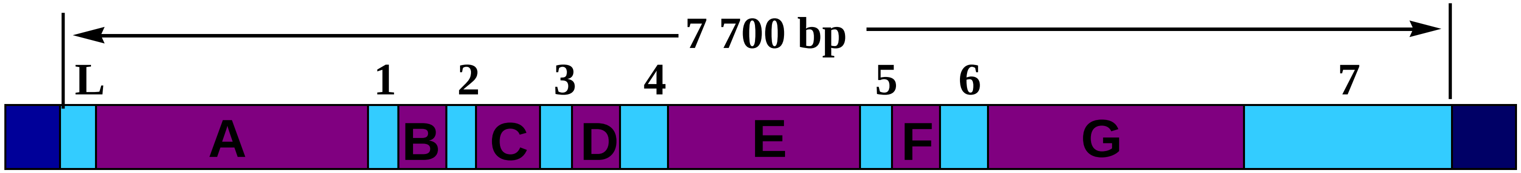
mRNA splicing



The matured mRNAs are much shorter than the DNA templates.

Split gene

The structural genes are composed of Coding (Exons) and Non-coding (Introns)regions that are alternatively separated.



A~G no-coding region **1~7 coding region**

Splicing of hnRNA / pre-mRNA

- **Introns (or) intervening sequences are the RNA sequences which do not code for the proteins.**

- **Introns usually start with 5´-GU.**

- **Introns usually end with 3´-AG.**

- **RNA splicing involves the removal introns from pre-mRNA and is carried out by small nuclear complexes Spliceosomes.**

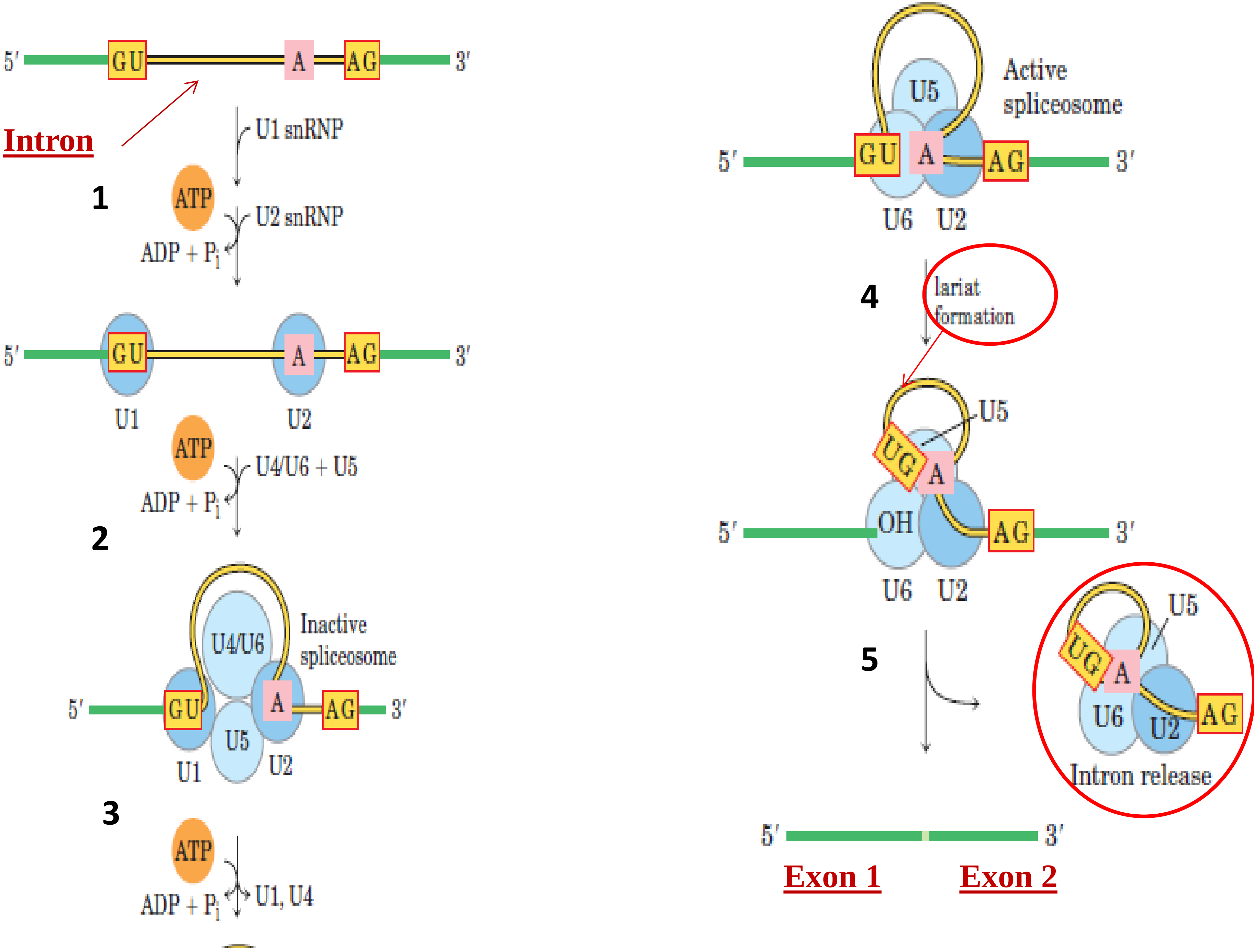
Spliceosome

- The spliceosome is a large Protein-RNA complex in which splicing of pre-mRNAs occurs.

- The spliceosome is made up of specialized RNA and Protein complexes called small nuclear RiboNucleoProteins (snRNPs, often pronounced "snurps").

- Each snRNP contains RNAs with 100 to 200 nucleotides long, known as small nuclear RNAs (snRNAs).

- **Five snRNAs (U1, U2, U4, U5, and U6) involved in splicing reactions are generally found in abundance in eukaryotic nuclei.**
- **Splice sites of Introns are recognized by snRNPs.**


5′
GU
A
AG
3′
Intron
1
U1 snRNP
ATP
U2 snRNP
ADP + P$_i$
5′
GU
A
AG
3′
U1
U2
ATP
U4/U6 + U5
ADP + P$_i$
2
U4/U6
Inactive spliceosome
5′
GU
A
AG
3′
U5
U1
U2
3
ATP
ADP + P$_i$
U1, U4
U5
Active spliceosome
5′
GU
A
AG
3′
U6
U2
4
lariat formation
U5
UG
A
OH
5′
AG
3′
U6
U2
5
U5
UG
A
U6
U2
AG
Intron release
5′
3′
Exon 1
Exon 2

Self splicing Introns (Group –I Introns)

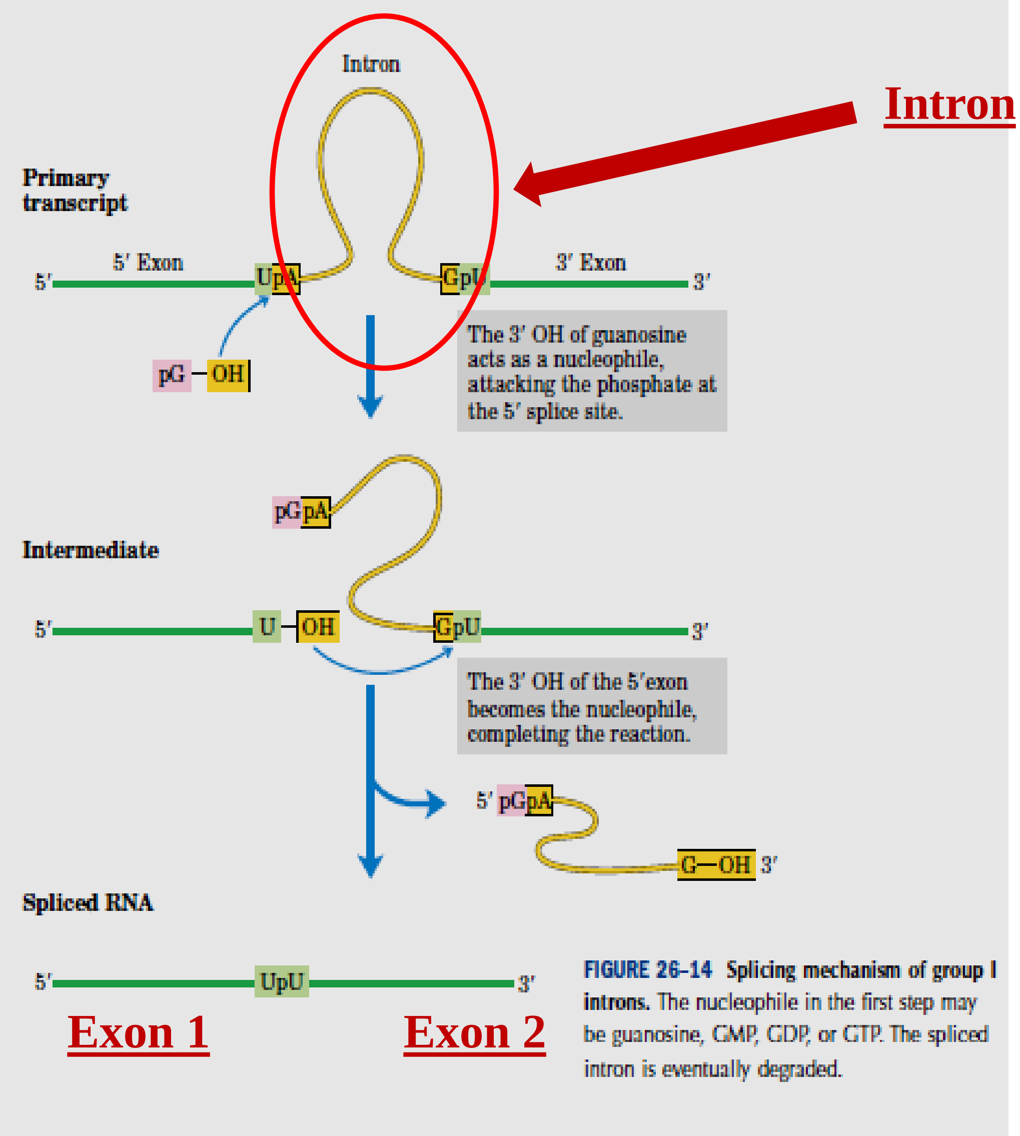
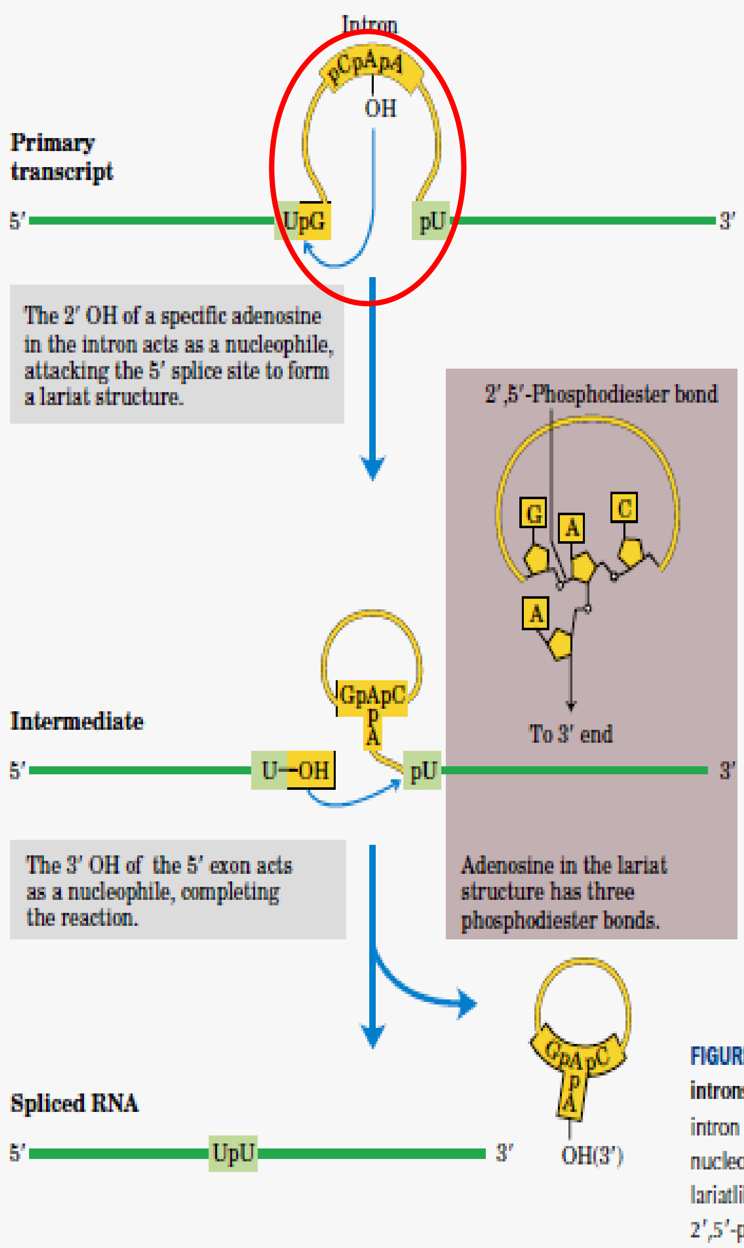


FIGURE 26–14 Splicing mechanism of group I introns. The nucleophile in the first step may be guanosine, GMP, GDP, or GTP. The spliced intron is eventually degraded.

Self splicing Introns (Group –II Introns)



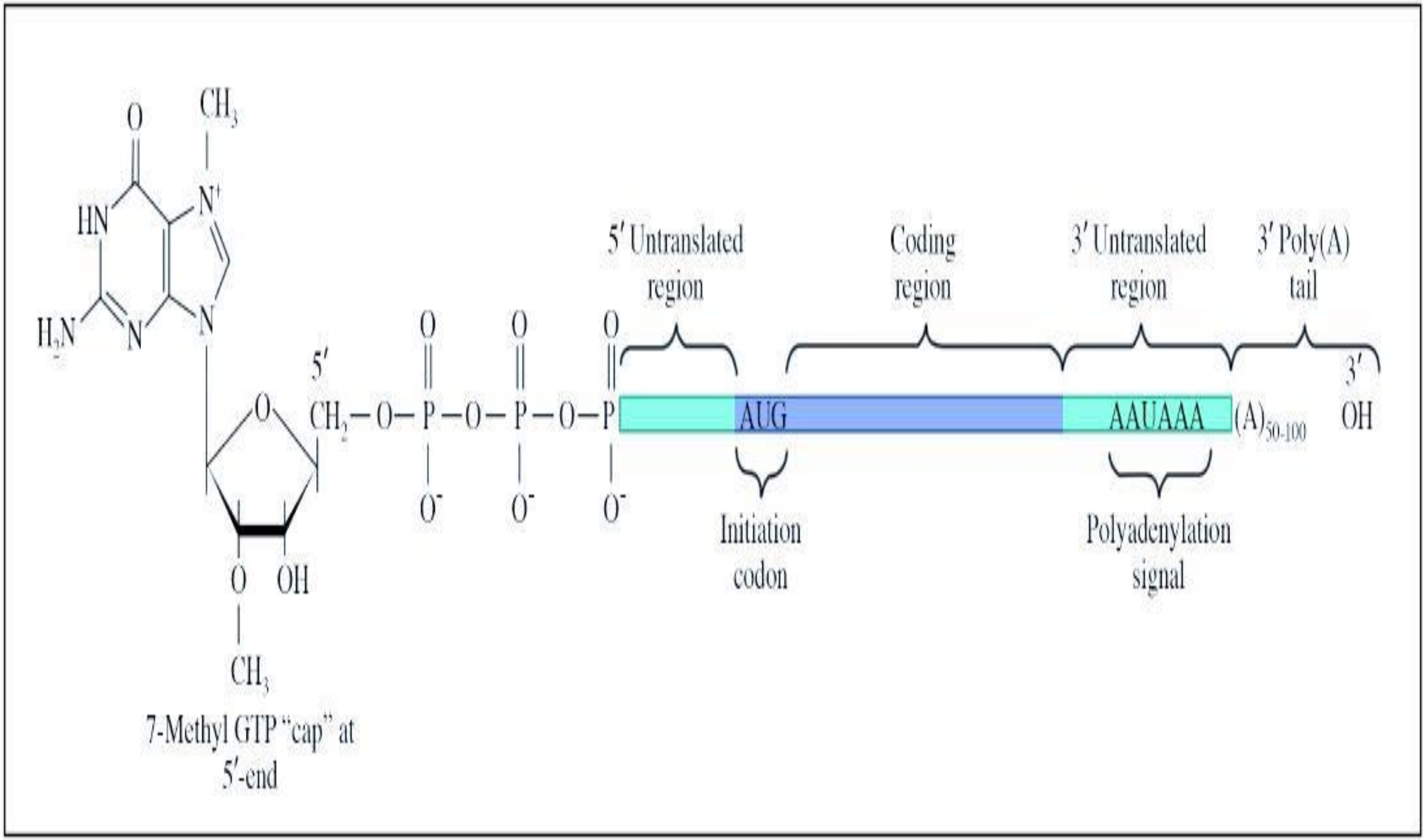
The 2′ OH of a specific adenosine in the intron acts as a nucleophile, attacking the 5′ splice site to form a lariat structure.

The 3′ OH of the 5′ exon acts as a nucleophile, completing the reaction.

Adenosine in the lariat structure has three phosphodiester bonds.

FIGURE 26–15 Splicing mechanism of group II introns. The chemistry is similar to that of group I intron splicing, except for the identity of the nucleophile in the first step and formation of a lariatlike intermediate, in which one branch is a 2′,5′-phosphodiester bond.

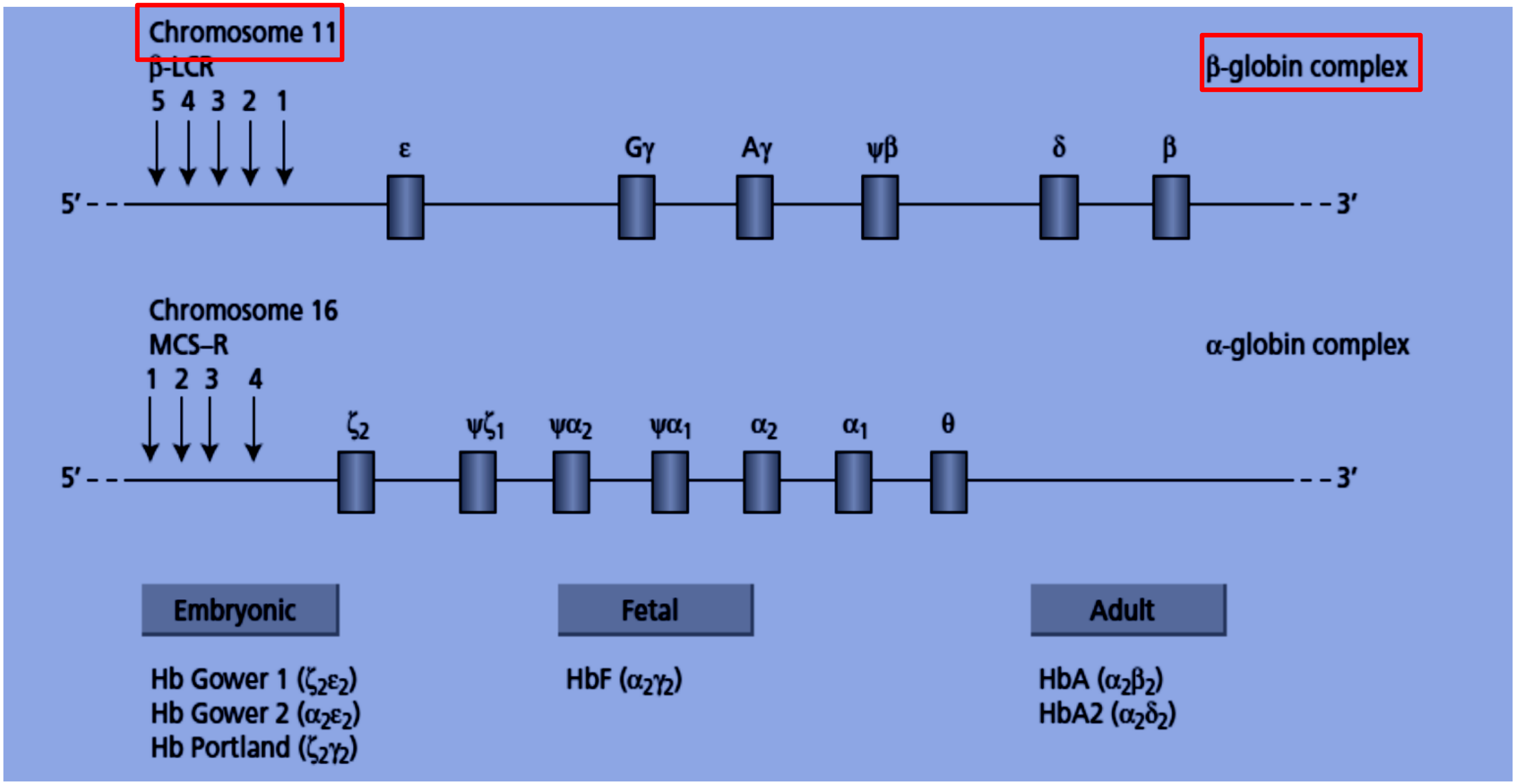
Eukaryotic m-RNA after modifications



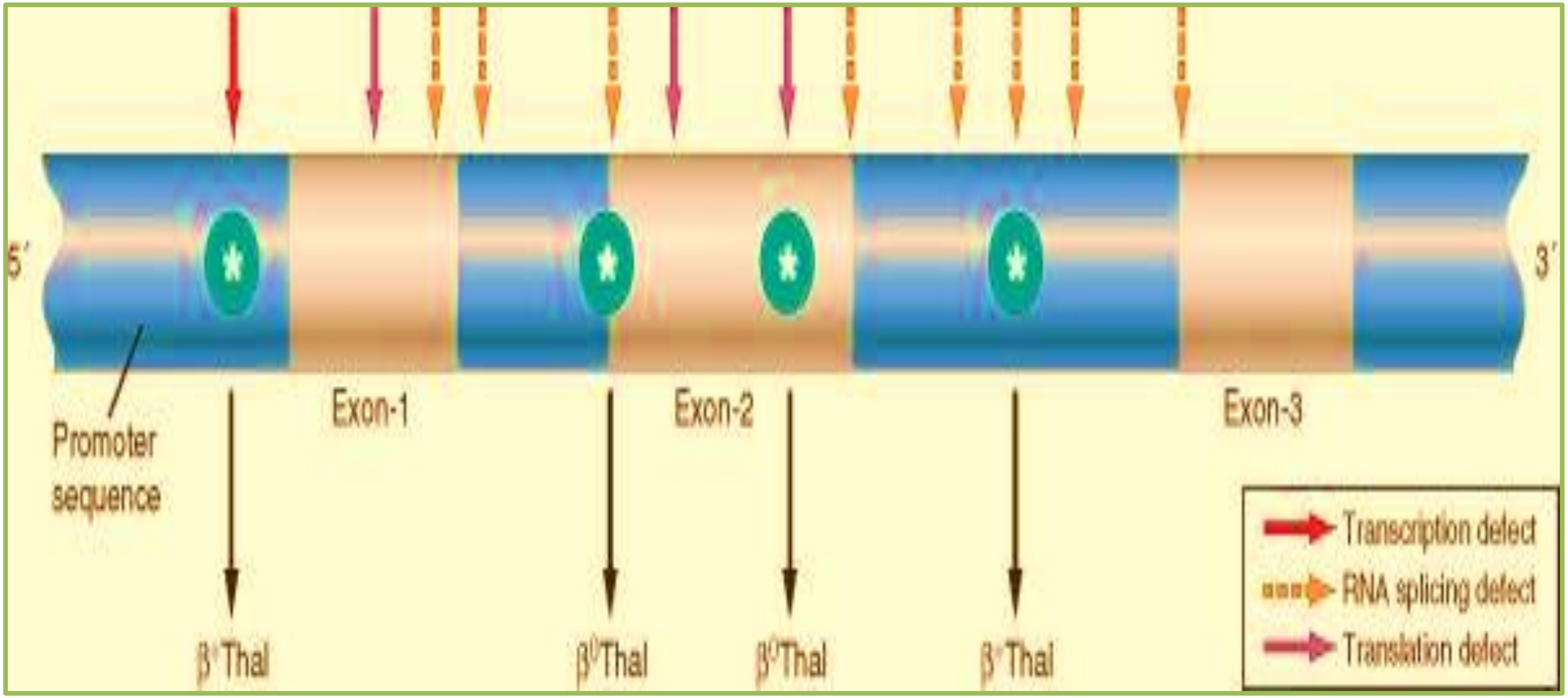
Splice site mutations

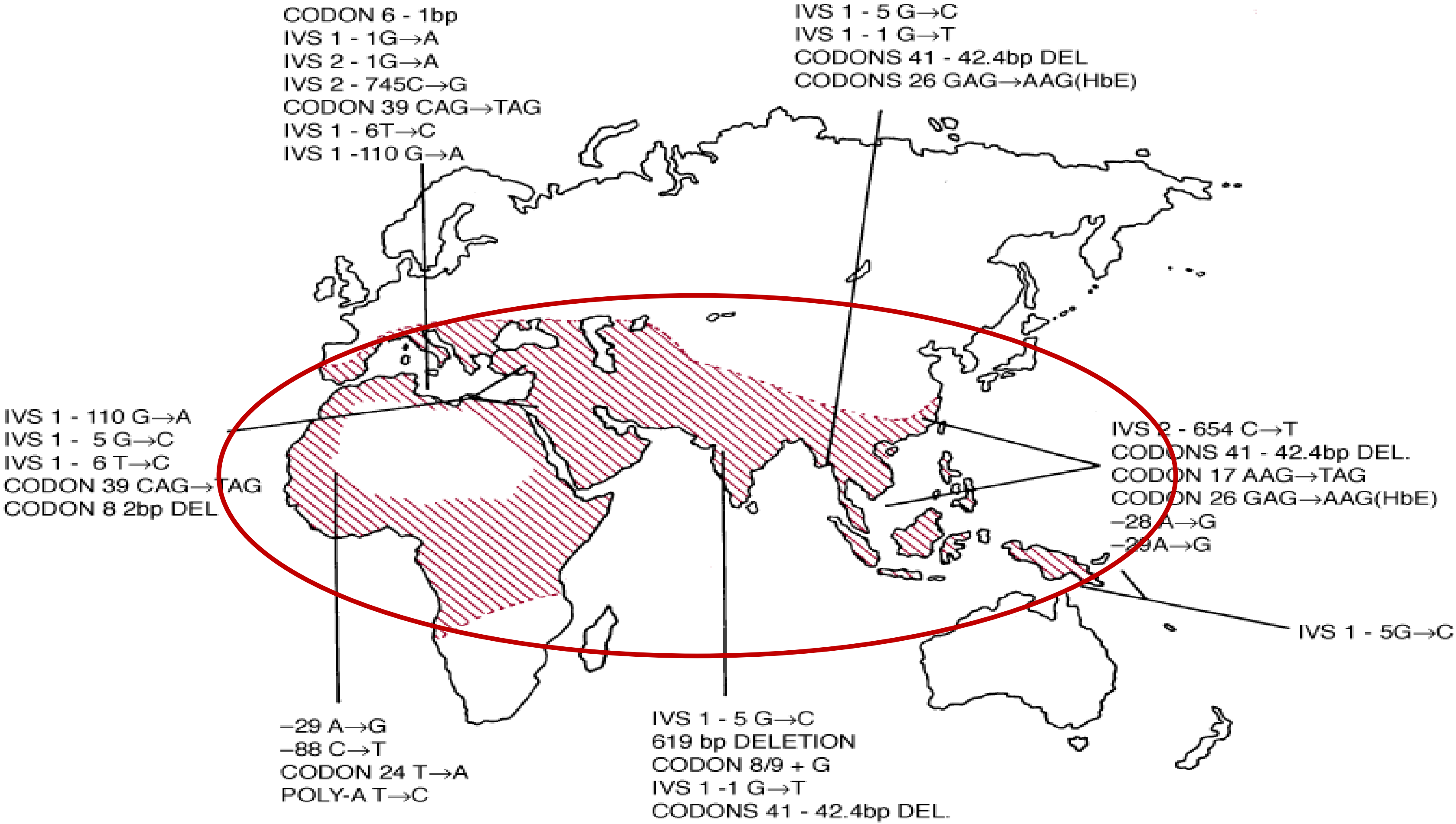
- Mutation at splice sites can lead to improper splicing and production of abberant proteins
- Eg: β - thalassemia
- β-subunit of hemoglobin is not formed in sufficient amount.
- It results from point mutation in β-globin gene where the G→A mutation occurs.
- This creates a new splice acceptor site nineteen nucleotides upstream from the normal splice acceptor
- A faulty beta-globin protein is made, leading to severe anemia.

Location of Globin genes



Distribution of β-globin gene mutations associated with β-thalassemia.





CODON 6 - 1bp
IVS 1 - 1G→A
IVS 2 - 1G→A
IVS 2 - 745C→G
CODON 39 CAG→TAG
IVS 1 - 6T→C
IVS 1 -110 G→A

IVS 1 - 5 G→C
IVS 1 - 1 G→T
CODONS 41 - 42.4bp DEL
CODONS 26 GAG→AAG(HbE)

IVS 1 - 110 G→A
IVS 1 - 5 G→C
IVS 1 - 6 T→C
CODON 39 CAG→TAG
CODON 8 2bp DEL

IVS 2 - 654 C→T
CODONS 41 - 42.4bp DEL.
CODON 17 AAG→TAG
CODON 26 GAG→AAG(HbE)
–28 A→G
–29A→G

IVS 1 - 5G→C

–29 A→G
–88 C→T
CODON 24 T→A
POLY-A T→C

IVS 1 - 5 G→C
619 bp DELETION
CODON 8/9 + G
IVS 1 -1 G→T
CODONS 41 - 42.4bp DEL.

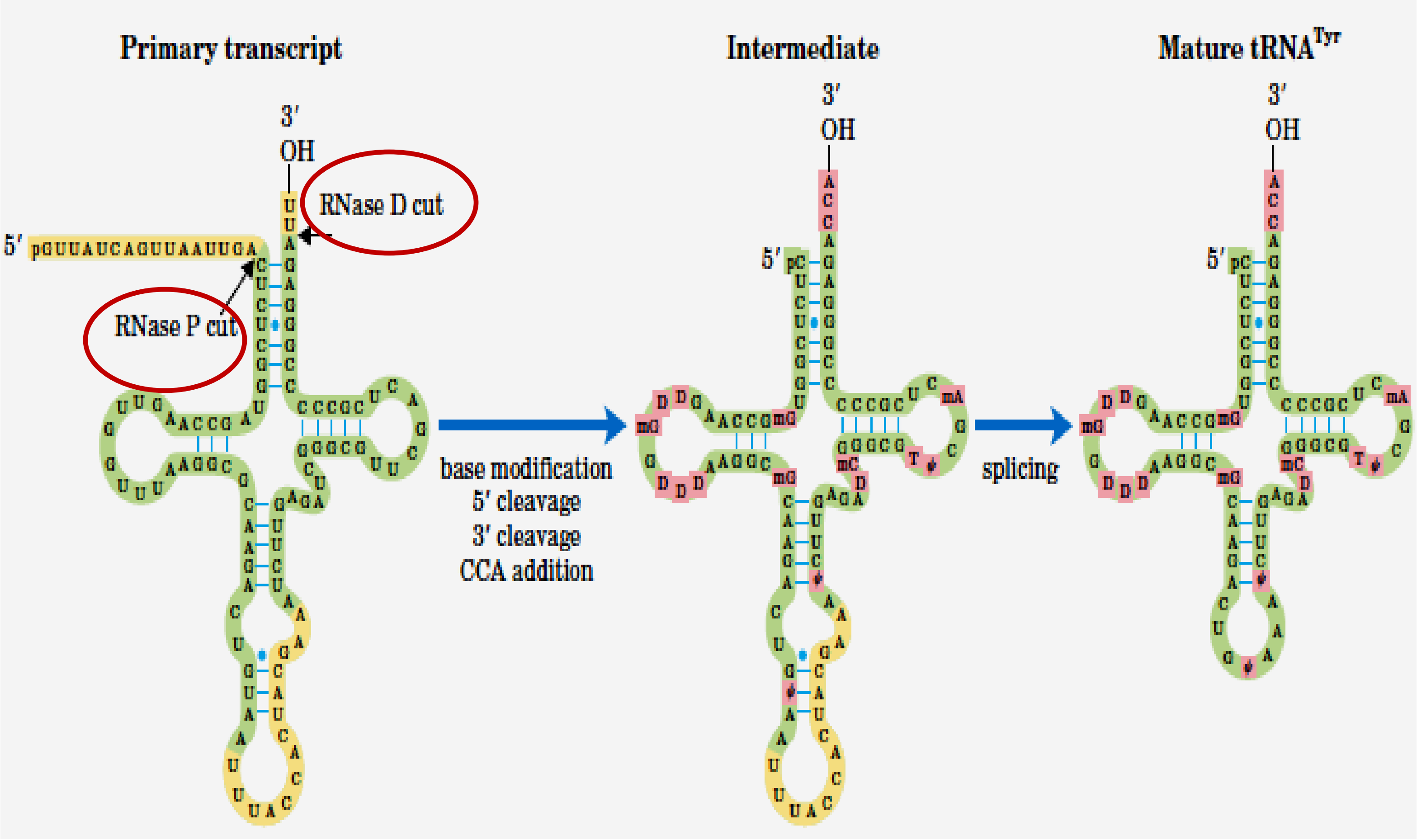
Source: Lichtman MA, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT: *Williams Hematology, 8th Edition*: http://www.accessmedicine.com

World distribution of β-thalassemia

Clinical syndromes in β-THALASSEMIAS

β-Thalassemia major	Severe; requires blood transfusions
β-Thalassemia intermedia	Severe but does not require regular blood transfusions
β-Thalassemia minor	Asymptomatic with mild or absent anemia; red cell abnormalities seen

Modification of tRNA

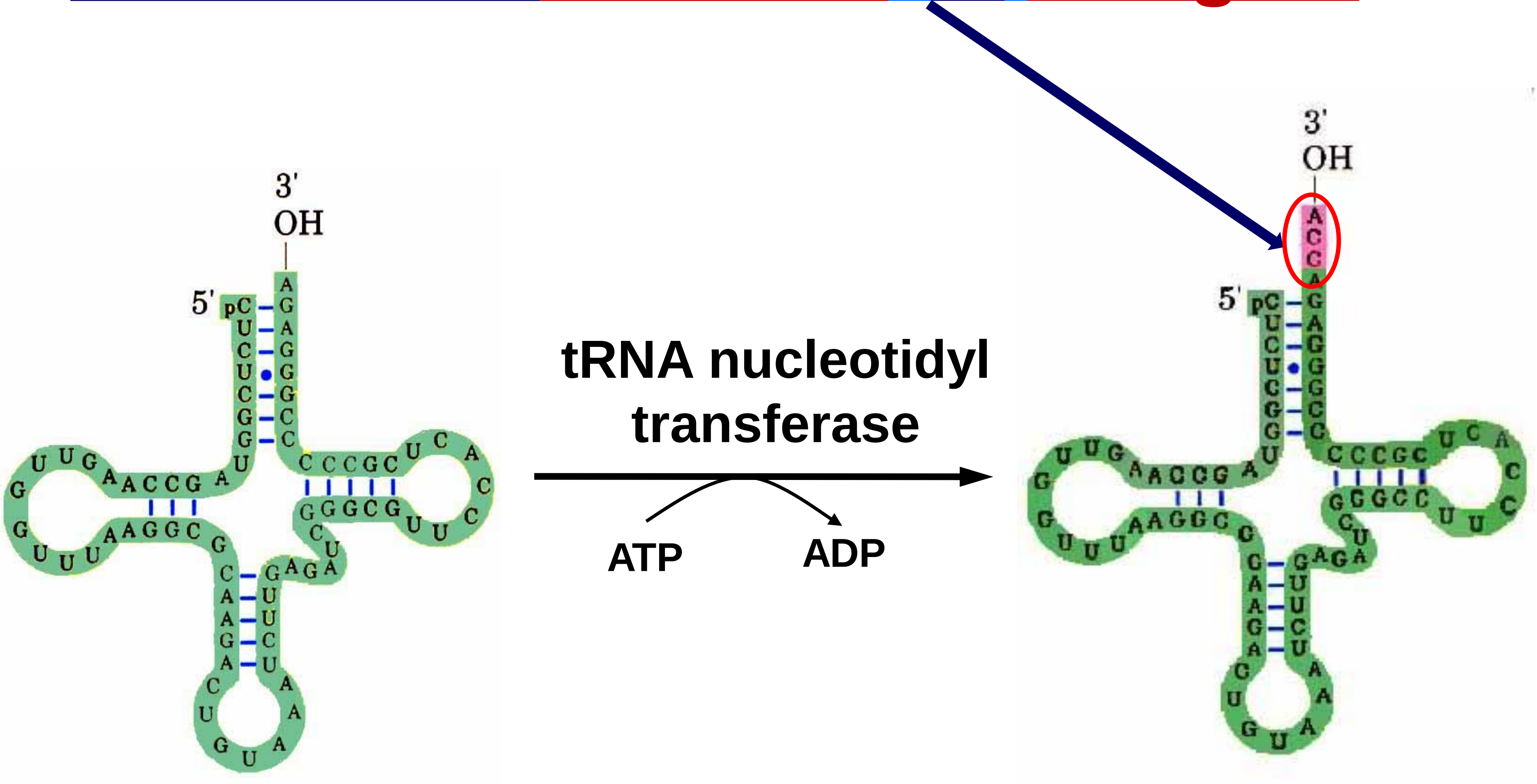


Endo- and exonucleases to generate ends of tRNA

- Endonuclease **RNase P** cleaves to generate the **5´ end**.

- Exonuclease **RNase D** trims 3′ to 5′, leaving the mature **3´ end**.

Addition of -CCA-OH at 3′ region



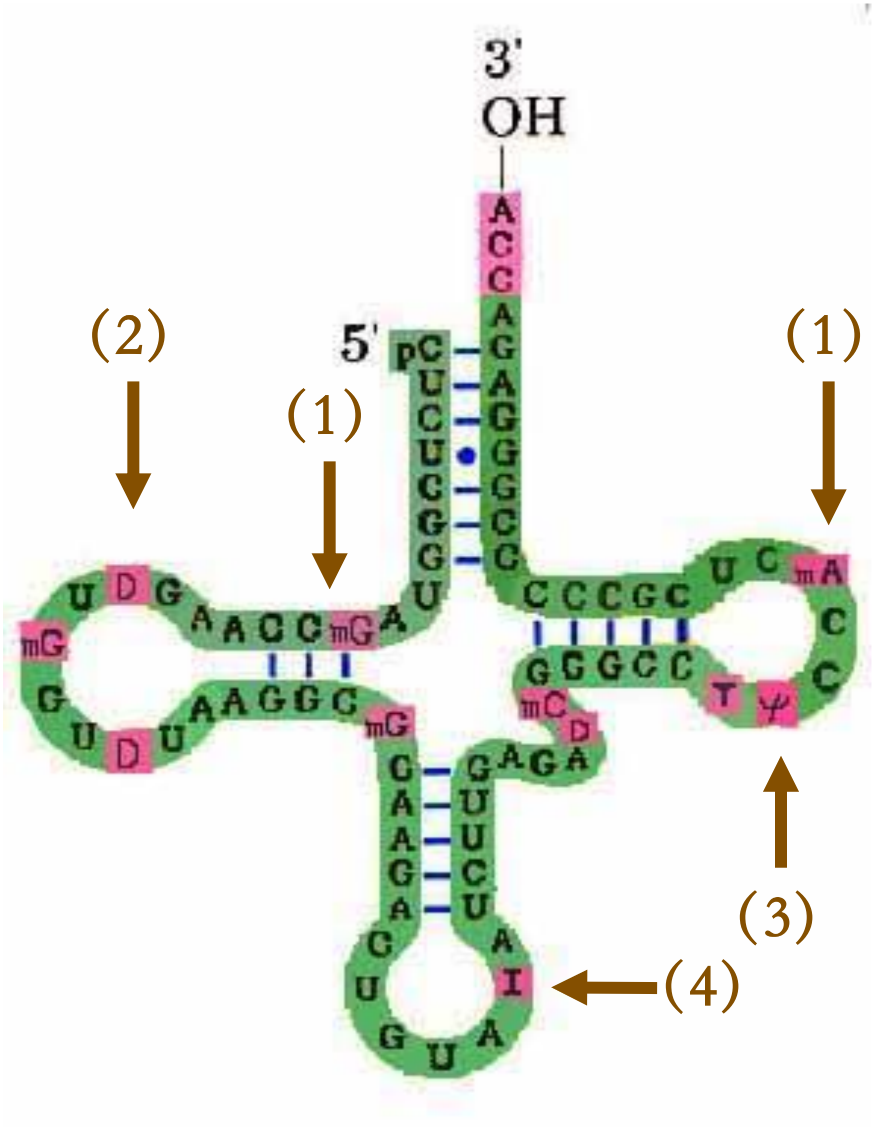
tRNA nucleotidyl transferase

ATP

ADP

At 3´-CCA region of tRNA an activated Amino acid will be attached during Protein Synthesis.

Base modifications



1. **Methylation**
   A→mA, G→mG

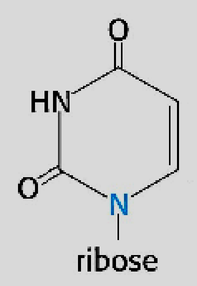
2. **Reduction**
   U→DHU

3. **Transversion**
   U→ψ

4. **Deamination**
   A→I

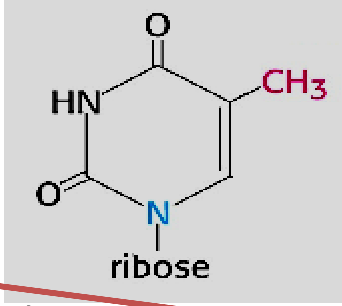
Modification of some bases

uridine

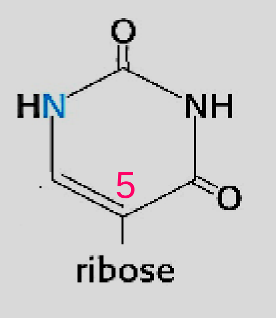


methylation

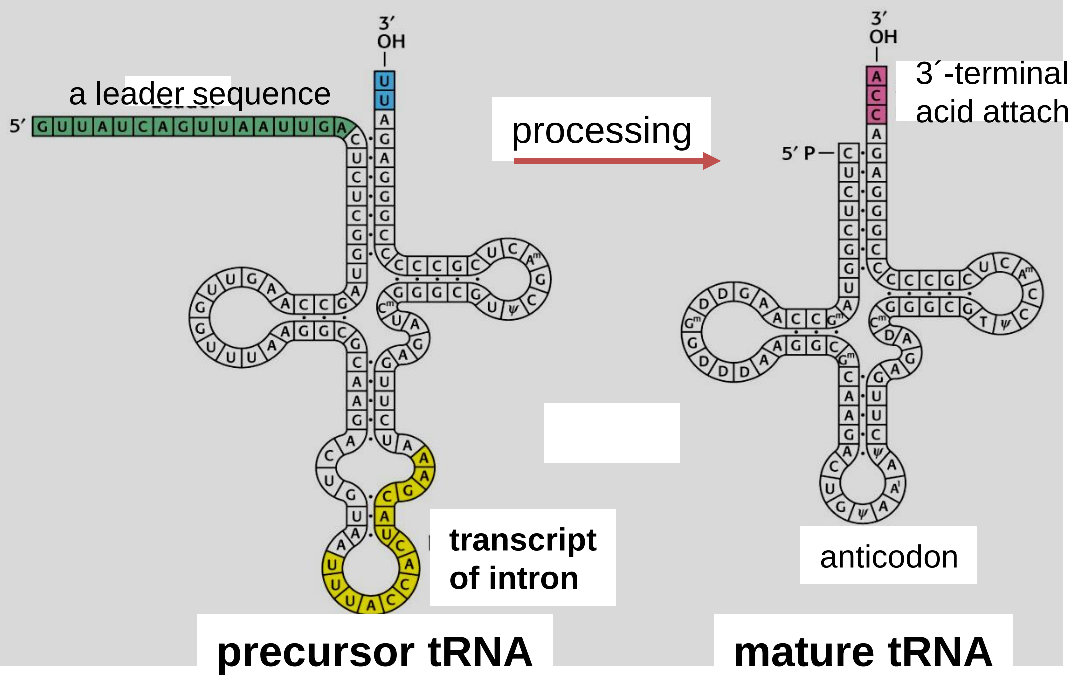
transformation of
the linkage to ribosyl



ribosyl thymine



pseudouridine (φ)



a leader sequence

processing

3´-terminal UU replaced by amino
acid attachment site CCA-3´-OH

transcript
of intron

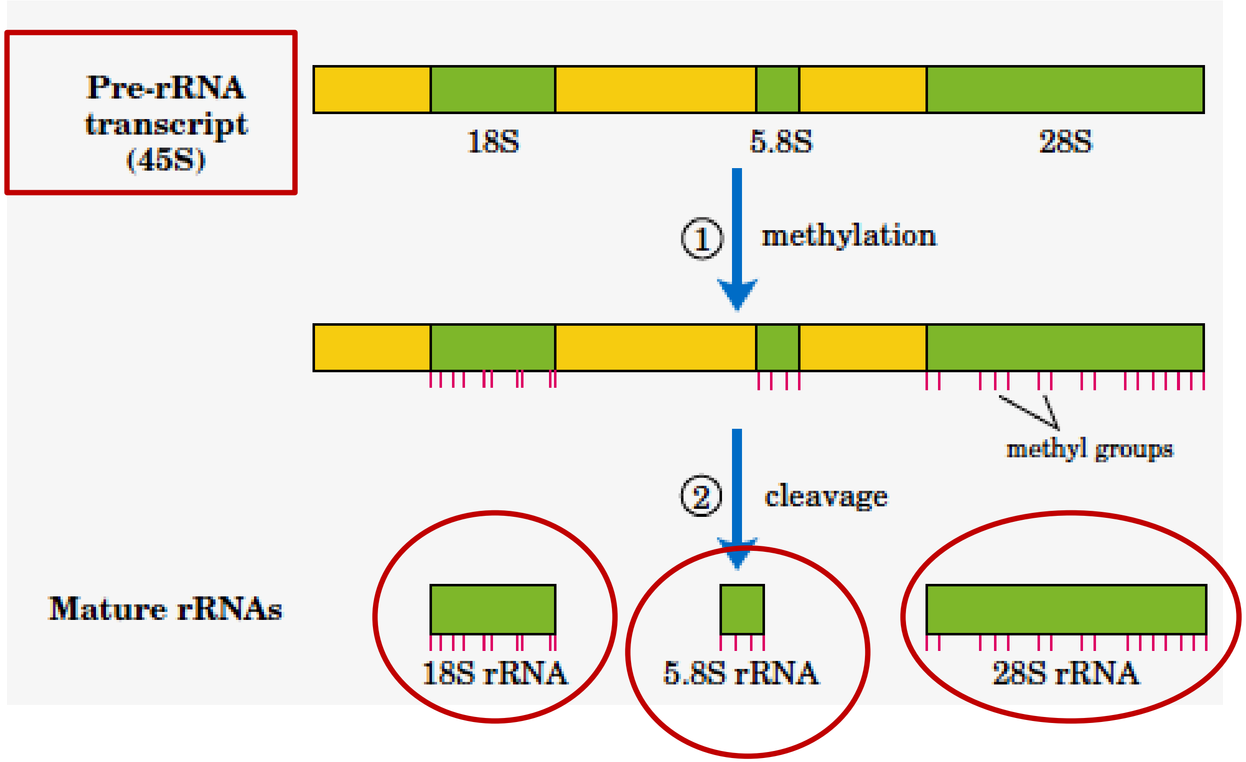
anticodon

precursor tRNA

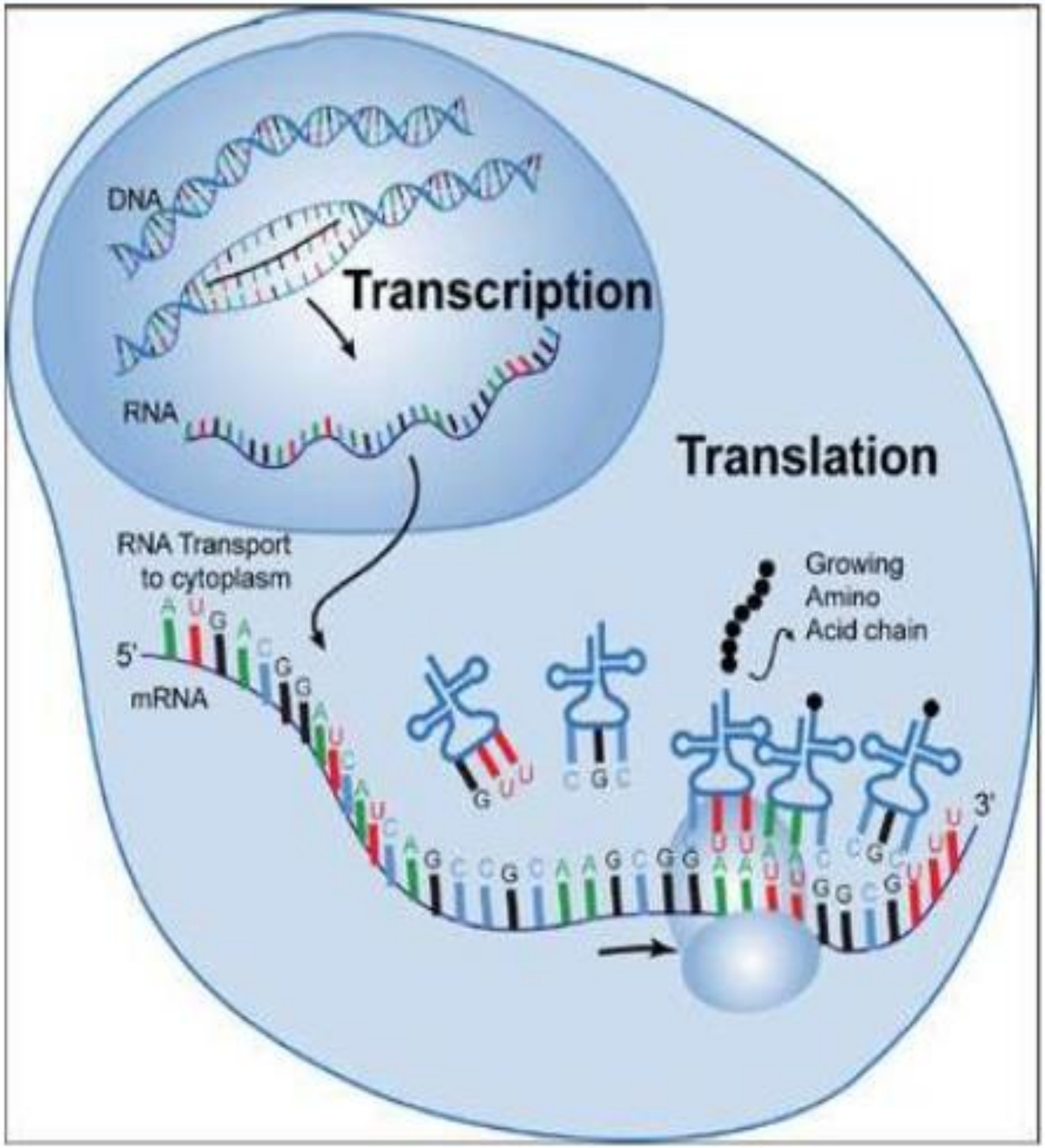
mature tRNA

Modification of rRNA

- **45S Pre-rRNA transcript in nucleus is the precursor of 3 kinds of rRNAs.**
- **The matured rRNA will be assembled with ribosomal proteins to form ribosomes that are exported to cytosolic space.**



TRADUZIONE


DNA
Transcription
RNA
Translation
RNA Transport to cytoplasm
Growing Amino Acid chain
5'
mRNA
3'
G U U
C G C

TRADUZIONE

Strutture coinvolte e sommario

t-RNA - Struttura e caratteristiche

- **Caratteristiche di base**

I ribosomi

- **Procariotici (componenti)**
- **Eucariotici (componenti)**
- **Funzioni delle unita' ribosomiali**

L'mRNA e il codice genetico

- **Caratteristiche dell'mRNA procariotico ed eucariotico**
- **Il codice genetico e le sue caratteristiche**
- **Wobbling & codice genetico**

- Aattivazione degli aminoacidic e caricamento del t-RNA
- Specificita’ e fedelta’ della reazione di acilazione
- Sintesi proteica nei procarioti
- Complesso di iniziazione e fattori di iniziazione
- Terminazione
- Antibiotici

Traduzione eucariotica

- Fattori di iniziazione, elongazione e terminazione eucariotiche
- Difterite & suoi effetti
- Ferro & e sintesi della globina

La traduzione e’ il processo con il quale una sequenza di triplette nucleotidiche in un RNA messaggero da origine a una specifica sequenza di amino acidi durante la sintesidi una catena polipeptidica (o) proteina.

- La traduzione avviene nel citoplasma e richiede il coinvolgimento di unita’ di sintesi proteica - Ribosomi, mRNA, t-RNA, Amino acidi, Aminoacyl-RNA syntetasi e molte altre proteine.

Il Dogma Centrale

5′-ATGCCTAGGTACCTATGA-3′
3′-TACGGATCCATGGATACT-5′

DNA

trascrizione

5′-AUGCCUAGGUACCUAUGA-3′

mRNA

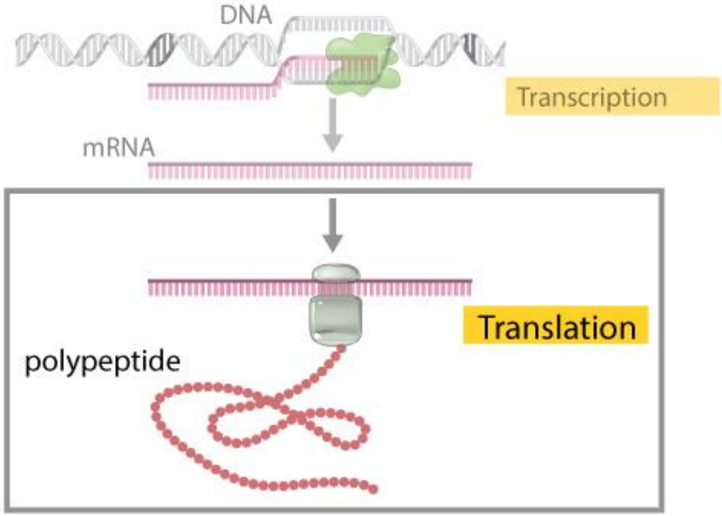
decodificata come

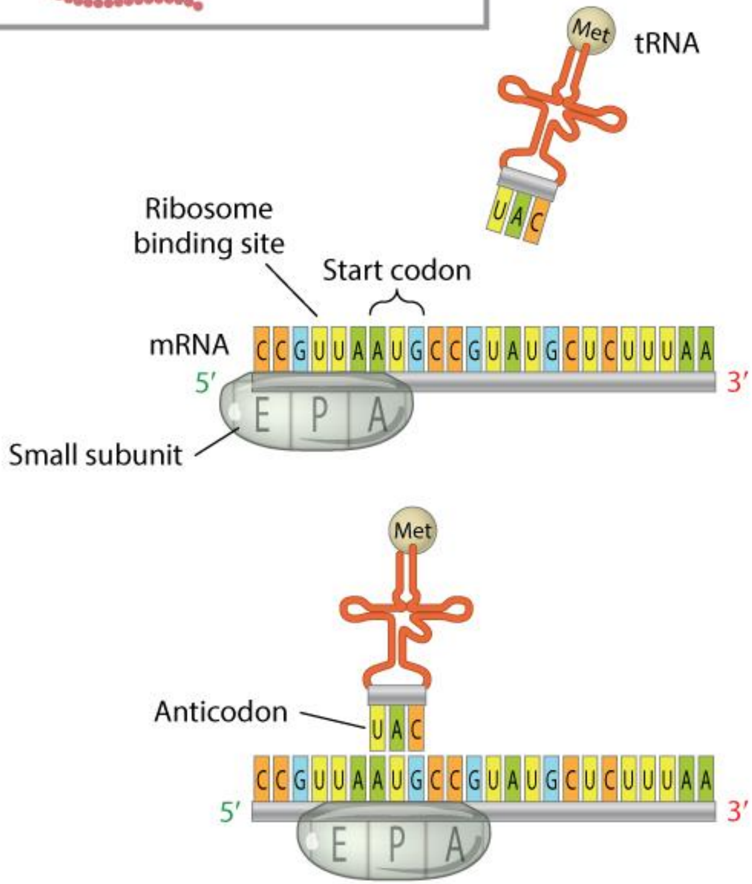
5′-AUG CCU AGG UAC CUA UGA-3′

Traduzione

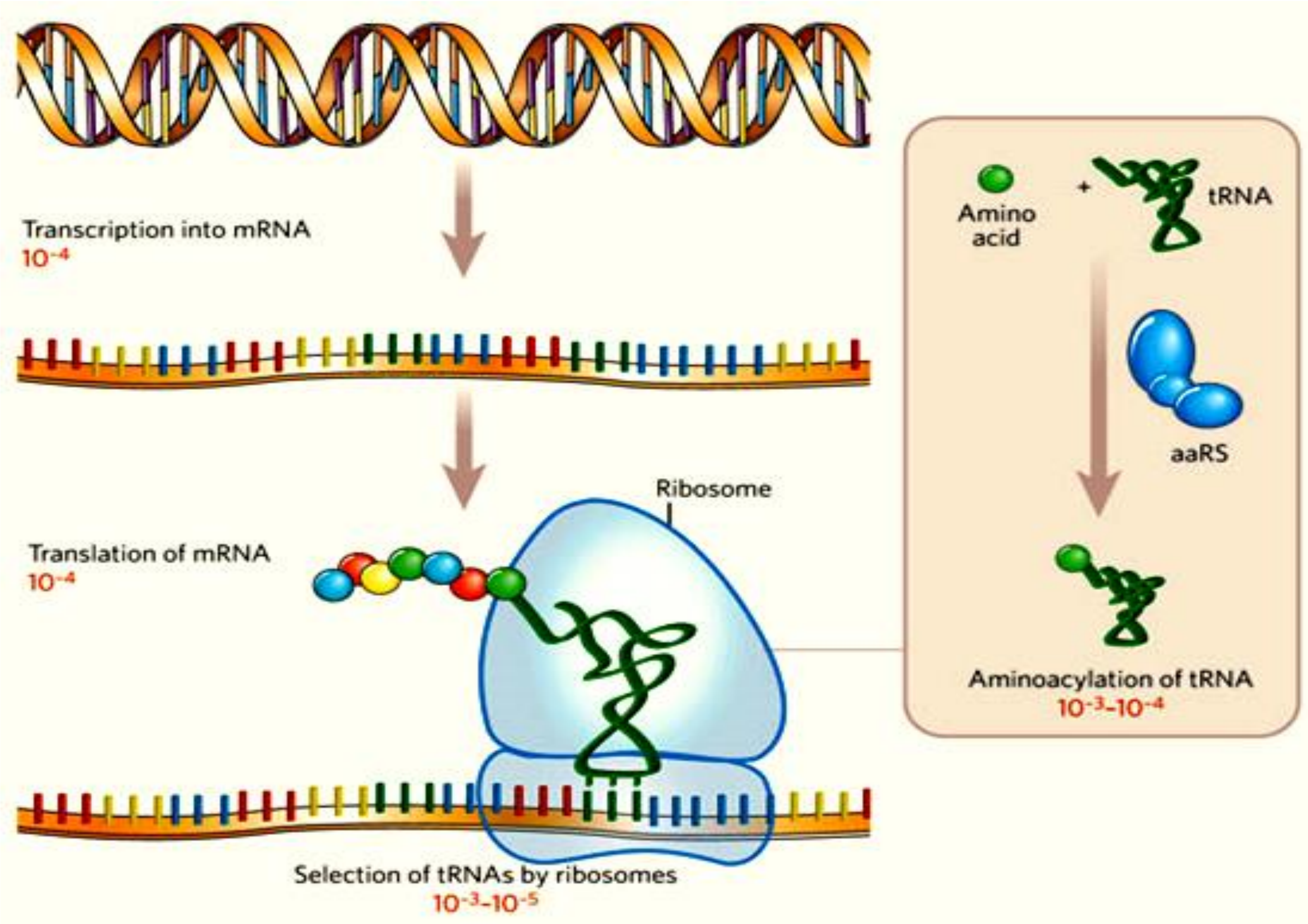
MET-PRO-ARG-TYR-LEU

Proteina





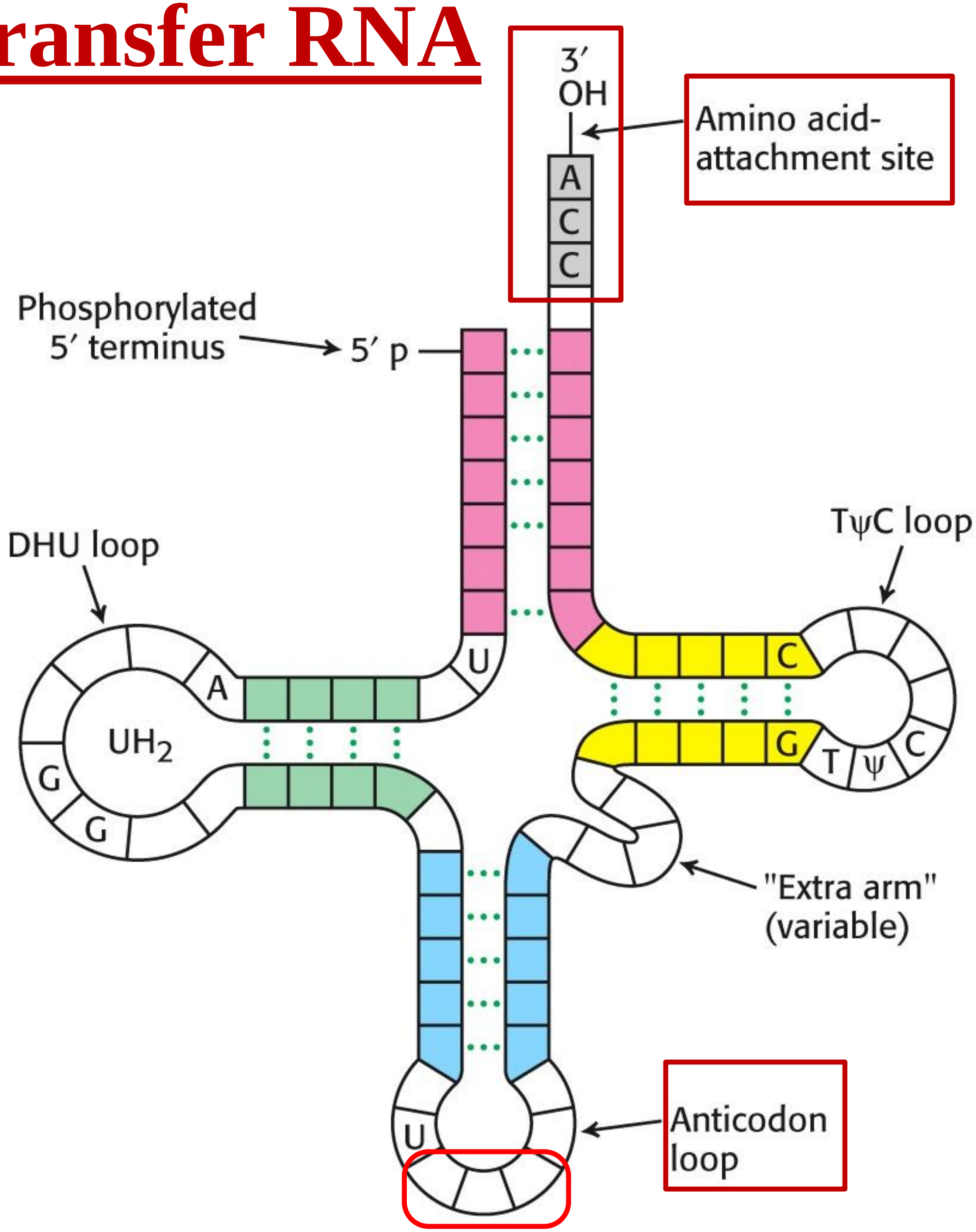
The translation initiation complex. When translation begins, the small subunit of the ribosome and an initiator tRNA molecule assemble on the mRNA transcript. The small subunit of the ribosome has three binding sites: an amino acid site (A), a polypeptide site (P), and an exit site (E). The initiator tRNA molecule carrying the amino acid methionine binds to the AUG start codon of the mRNA transcript at the ribosome's P site where it will become the first amino acid incorporated into the growing polypeptide chain. Here, the initiator tRNA molecule is shown binding after the small ribosomal subunit has assembled on the mRNA; the order in which this occurs is unique to prokaryotic cells. In eukaryotes, the free initiator tRNA first binds the small ribosomal subunit to form a complex. The complex then binds the mRNA transcript, so that the tRNA and the small ribosomal subunit bind the mRNA simultaneously.

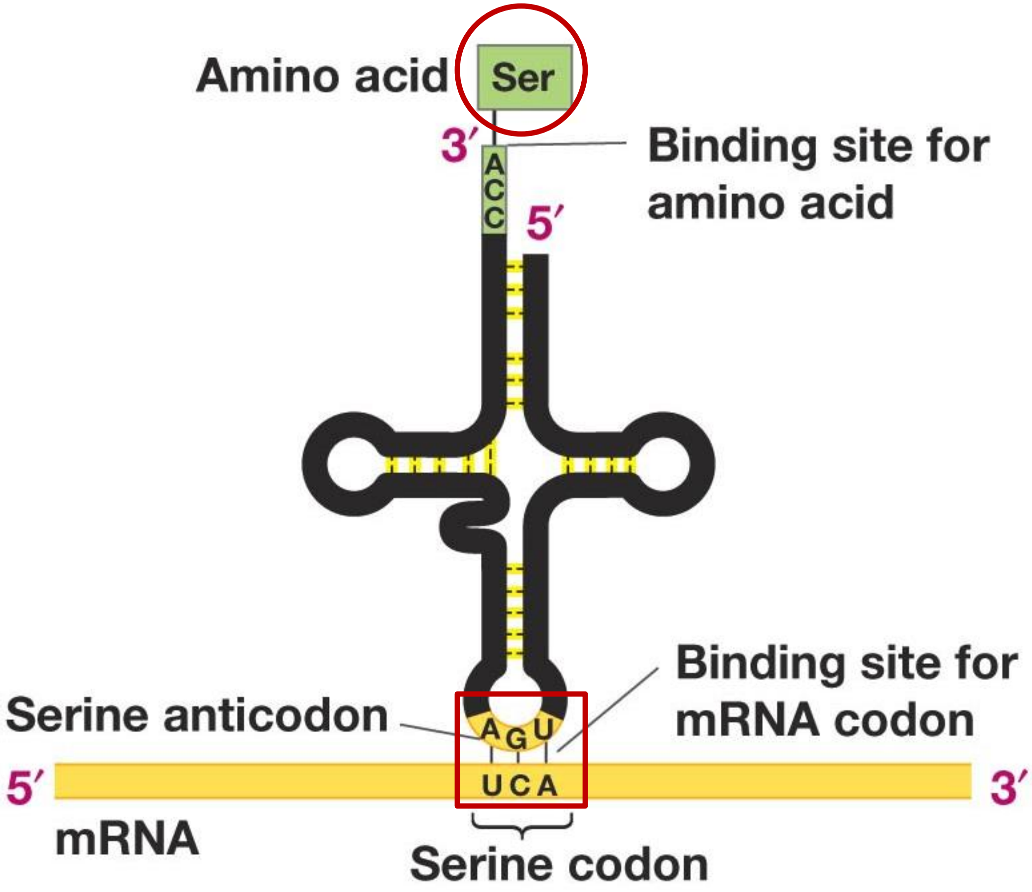

Transcription into mRNA
10^{-4}
Translation of mRNA
10^{-4}
Ribosome
Selection of tRNAs by ribosomes
10^{-3}–10^{-5}
Amino acid
+
tRNA
aaRS
Aminoacylation of tRNA
10^{-3}–10^{-4}

Componenti della sintesi proteica

- **mRNA (ORF)**
- **Ribosomi**
- **Amino acids (20)**
- **tRNA**
- **Mg2^{+}**
- **Amino acyl tRNA Synthetases (I and II)**
- **Fattori di iniziazione, elungazione e terminazione**

transfer RNA





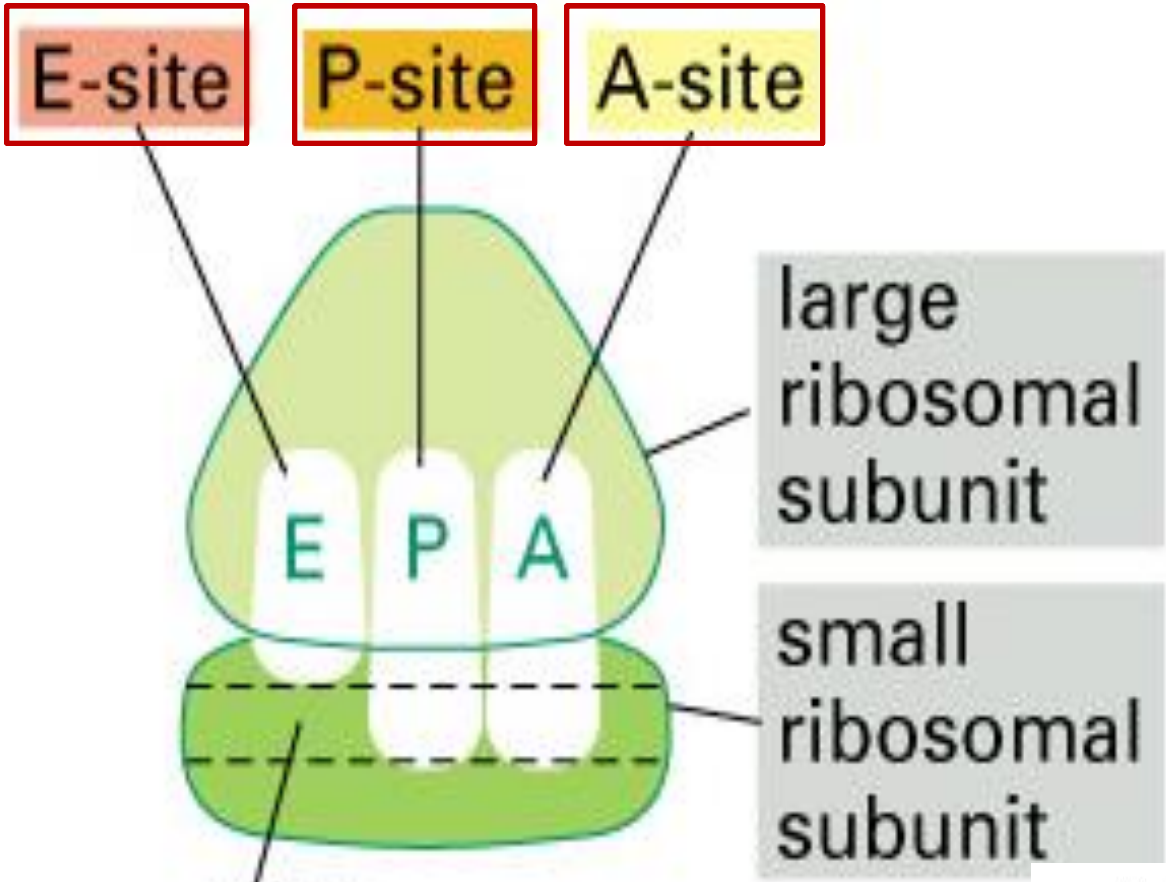
- **3’ end of tRNA**: **binding site for amino acids**.
- **Anticodon loop at opposite end**:
  - **Interacts with complementary codon on mRNA**.

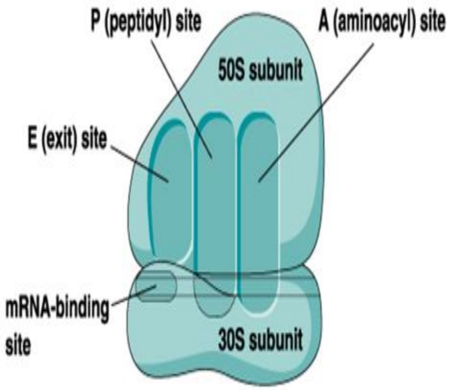
Ribosomi

- Ribosomes are the macromolecular complex that directs the synthesis of proteins.

- These are the sites of protein synthesis, having
  - 30% - 40% protein
  - 60% - 70% RNA (rRNA)

  - Each Ribosome having 2 ribosomal subunits –larger and smaller.


E-site
P-site
A-site
E
P
A
large ribosomal subunit
small ribosomal subunit
mRNA-binding site


P (peptidyl) site
A (aminoacyl) site
50S subunit
E (exit) site
mRNA-binding site
30S subunit

Un ribosoma ha tre tRNA binding sites

1) Sito A – binding site per il primo tRNA aminoacilato

1) Sito P – binding site per il peptidyl tRNA

1) Sito E – binding site per il tRNA scarico

Questi siti sono presenti sulla superfiche di interfaccia tra la piccola e la grande subunita’ del ribosoma.

Ribosoma Procariotico (70S)

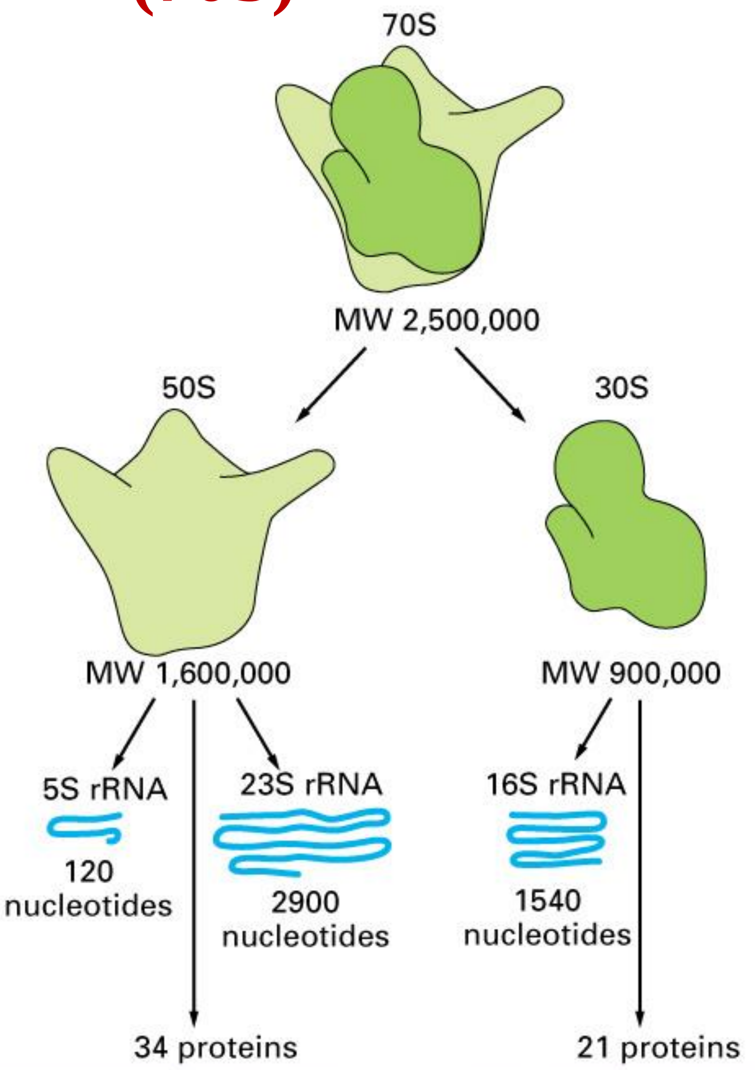


Figure 6–63 part 1 of 2. Molecular Biology of the Cell, 4th Editior

Ribosoma Eucariotico (80S)

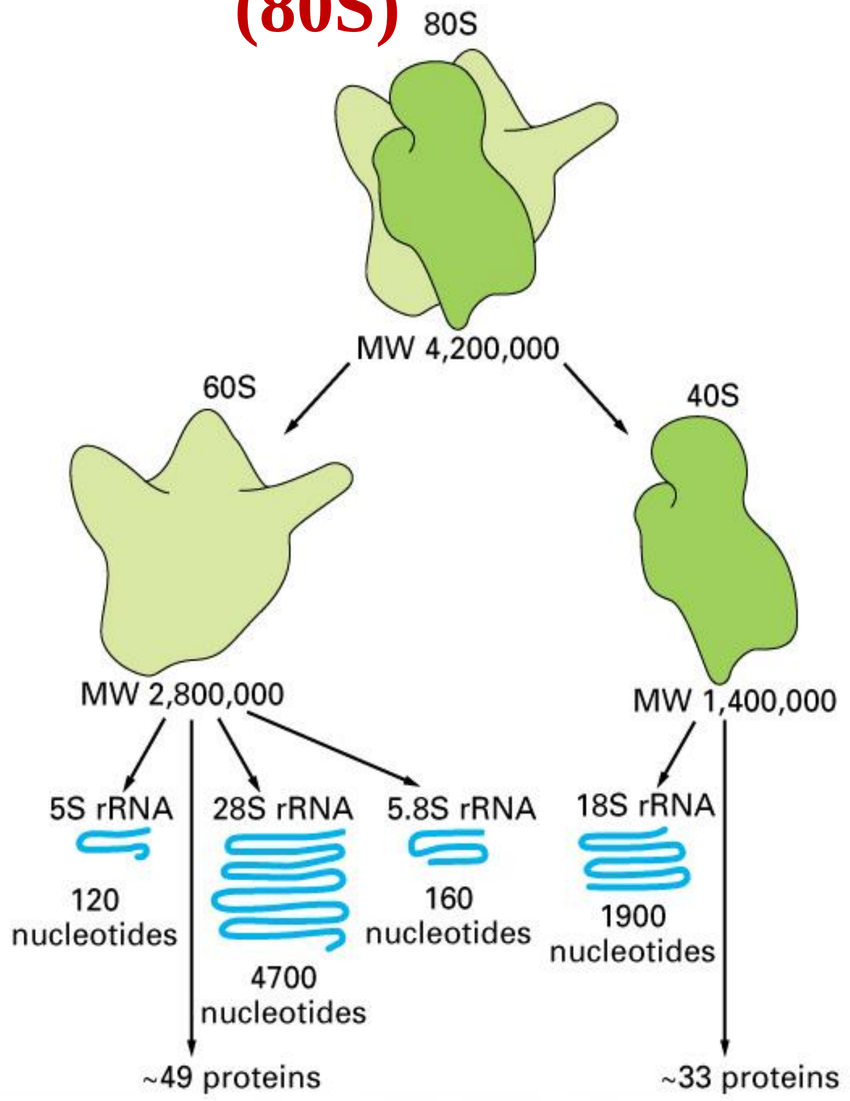
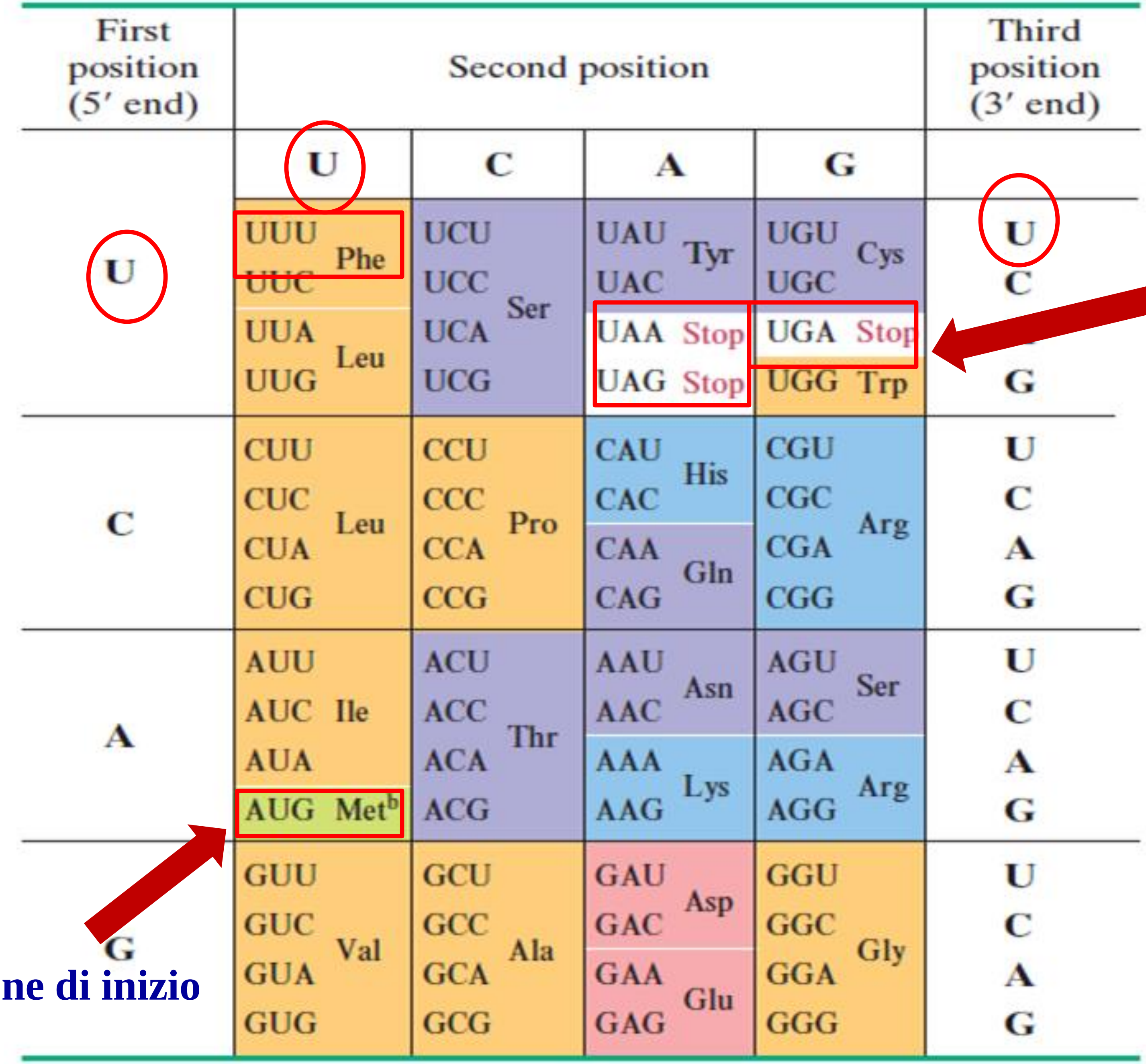


Figure 6–63 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

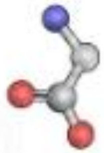
Il Codice Genetico



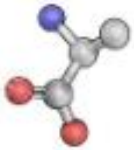
First position (5′ end)	Second position				Third position (3′ end)
	U	C	A	G	
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC	UCC	UAC	UGC	C
	UUA Leu	UCA	UAA Stop	UGA Stop	
	UUG	UCG	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC	CCC	CAC	CGC	C
	CUA	CCA	CAA Gln	CGA	A
	CUG	CCG	CAG	CGG	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC	ACC	AAC	AGC	C
	AUA	ACA	AAA Lys	AGA Arg	A
	AUG Met[b]	ACG	AAG	AGG	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC	GCC	GAC	GGC	C
	GUA	GCA	GAA Glu	GGA	A
	GUG	GCG	GAG	GGG	G

Codoni di stop

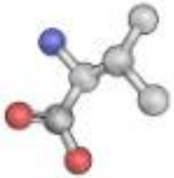
Codone di inizio



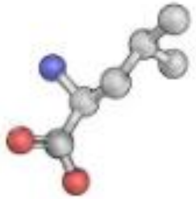
glycine (Gly, G)



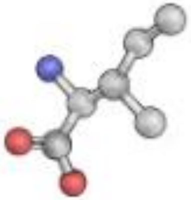
L-alanine (Ala, A)



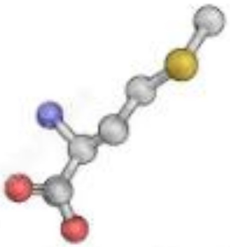
L-valine (Val, V)



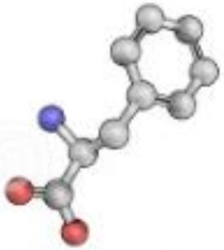
L-leucine (Leu, L)



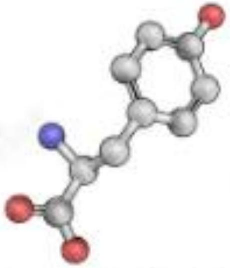
L-isoleucine (Ile, I)



L-methionine (Met, M)

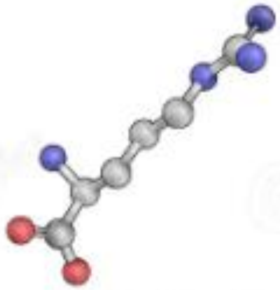


L-phenylalanine (Phe, F)

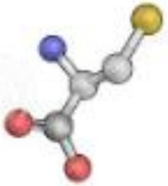


L-tyrosine (Tyr, Y)

L-tryptophan (Trp, W)

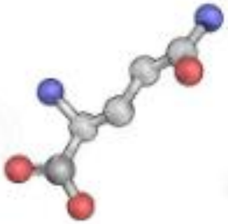


L-arginine (Arg, R)

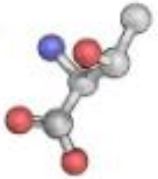


L-cysteine (Cys, C)

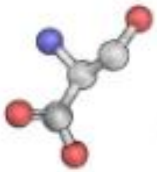
L-asparagine (Asn, N)



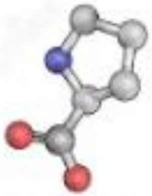
L-glutamine (Gln, Q)



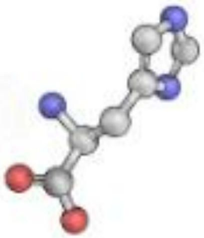
L-threonine (Thr, T)



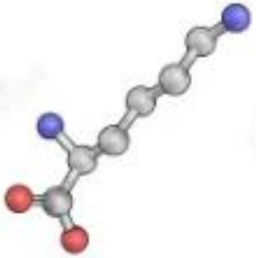
L-serine (Ser, S)



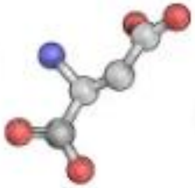
L-proline (Pro, P)



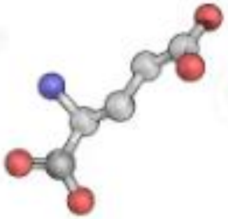
L-histidine (His, H)



L-lysine (Lys, K)

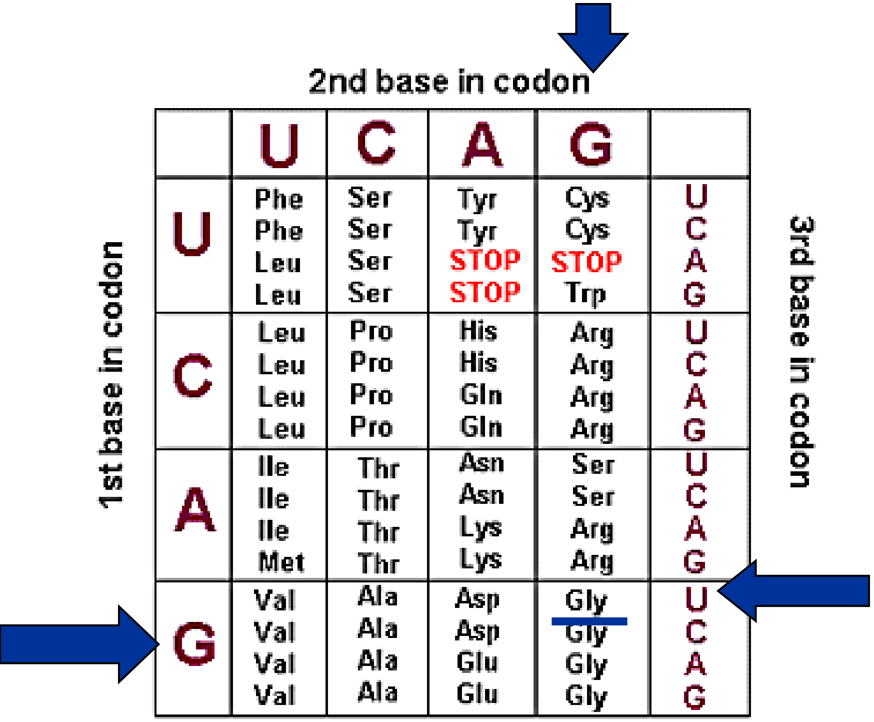


L-aspartic acid (Asp, D)



L-glutamic acid (Glu, E)

Codice genetico



2nd base in codon

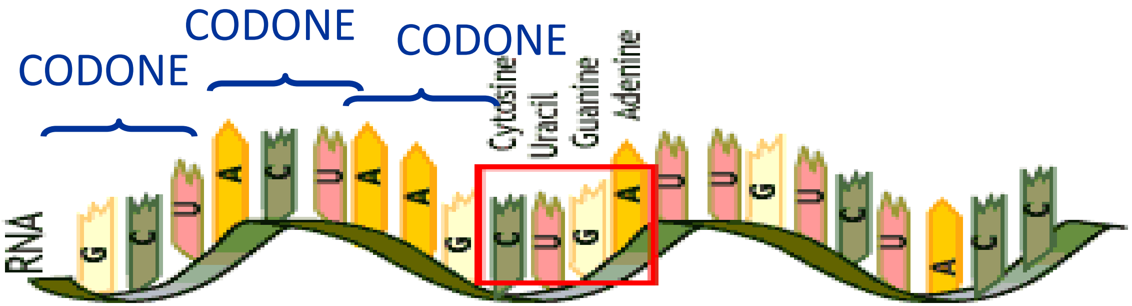
1st base in codon

3rd base in codon

	U	C	A	G	
U	Phe	Ser	Tyr	Cys	U
	Phe	Ser	Tyr	Cys	C
	Leu	Ser	STOP	STOP	A
	Leu	Ser	STOP	Trp	G
C	Leu	Pro	His	Arg	U
	Leu	Pro	His	Arg	C
	Leu	Pro	Gln	Arg	A
	Leu	Pro	Gln	Arg	G
A	Ile	Thr	Asn	Ser	U
	Ile	Thr	Asn	Ser	C
	Ile	Thr	Lys	Arg	A
	Met	Thr	Lys	Arg	G
G	Val	Ala	Asp	Gly	U
	Val	Ala	Asp	Gly	C
	Val	Ala	Glu	Gly	A
	Val	Ala	Glu	Gly	G

Nonostante ci siano solo 20 aminoacidi, ci sono 64 possibili codoni.

4 X 4 X 4 = 64 combinazioni possibili



Primo NUCLEOTIDE

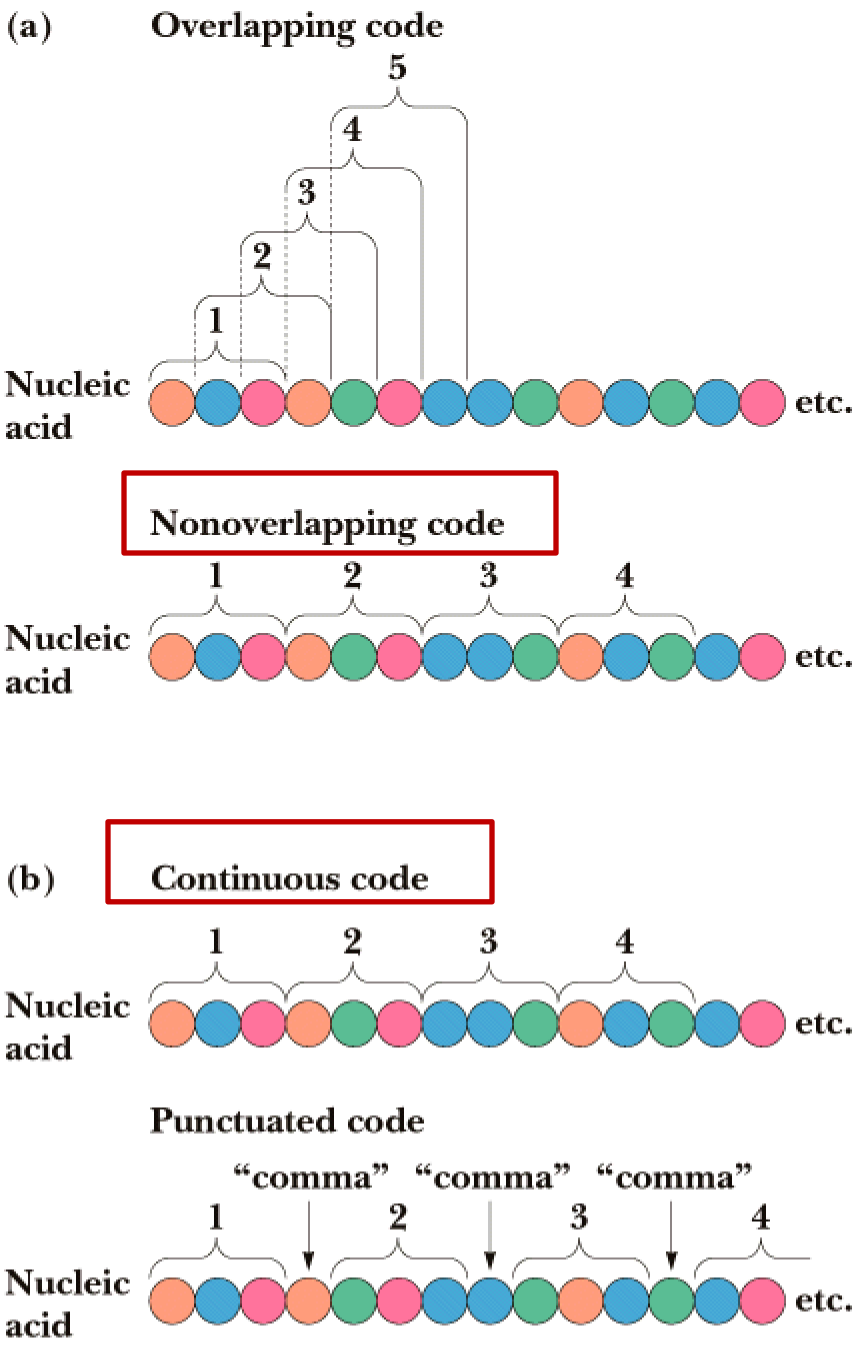
Terzo NUCLEOTIDE

G G U = Glicina

Secondo NUCLEOTIDE

Characteristics of Genetic Code

- Triplet Codons
- Universal
- Non-overlapping
- Unambiguous
- Degenerate
- Stop or termination or nonsense codons



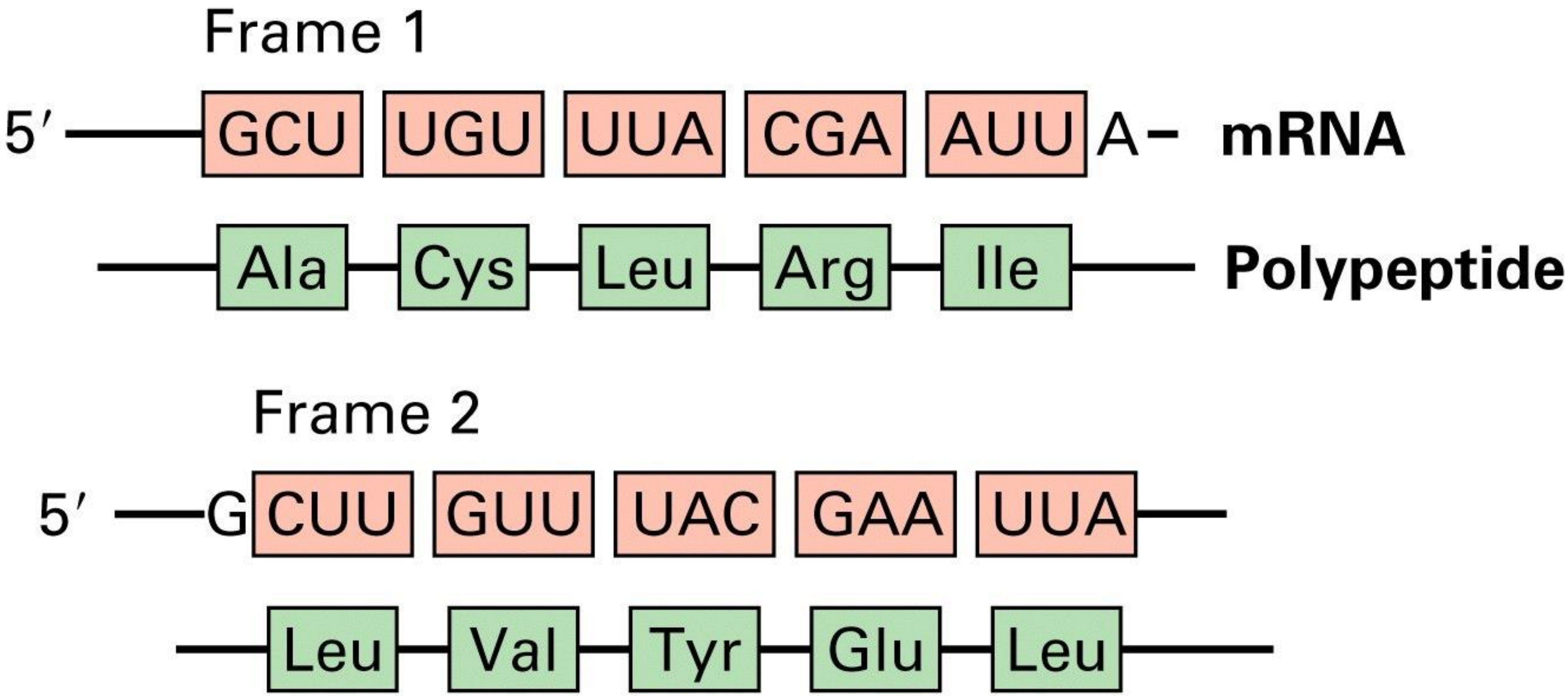
(a) Overlapping code

Nonoverlapping code

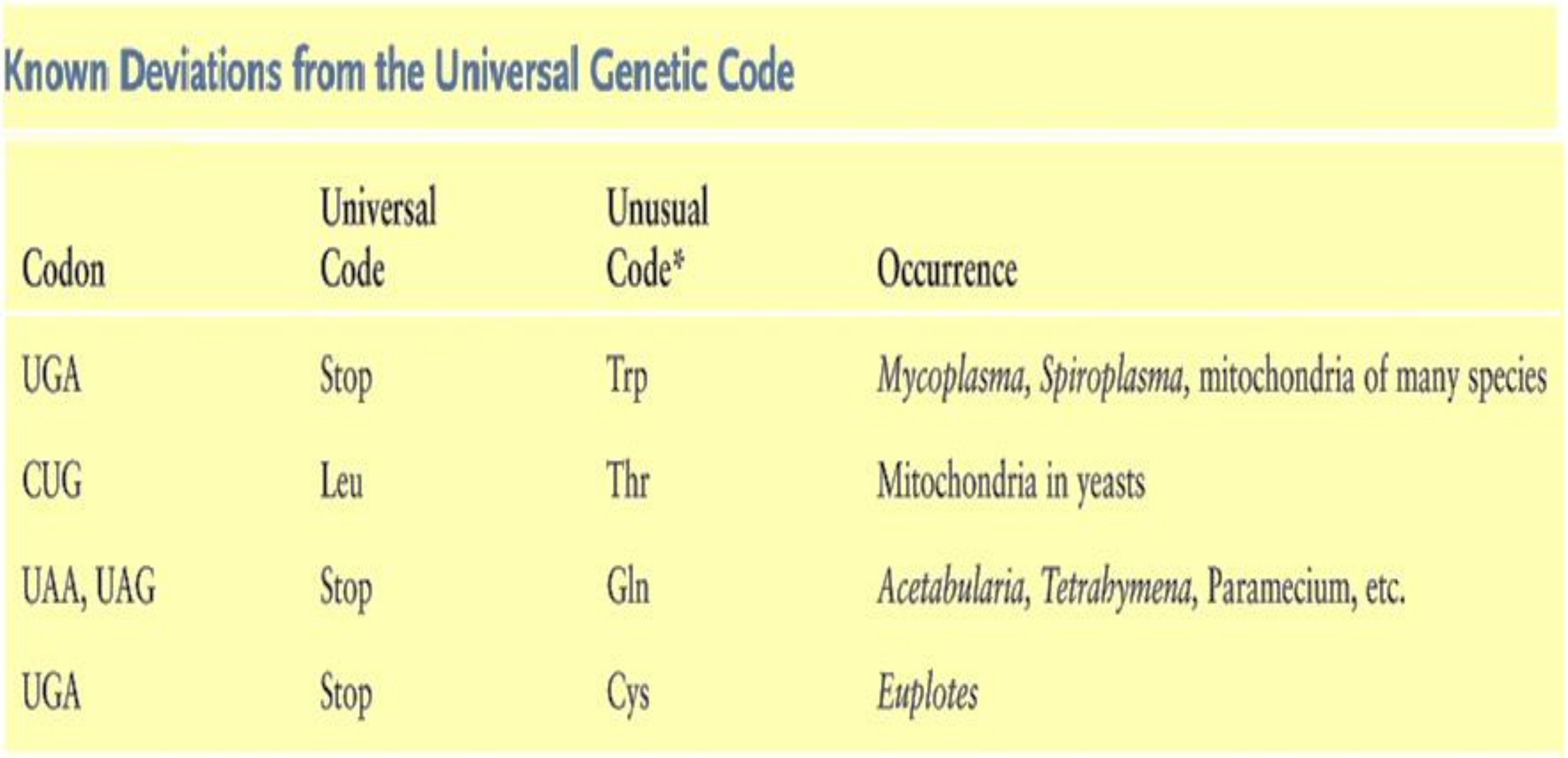
(b) Continuous code

Punctuated code

Un codice di tre lettere puo’ essere letto con vari reading frames

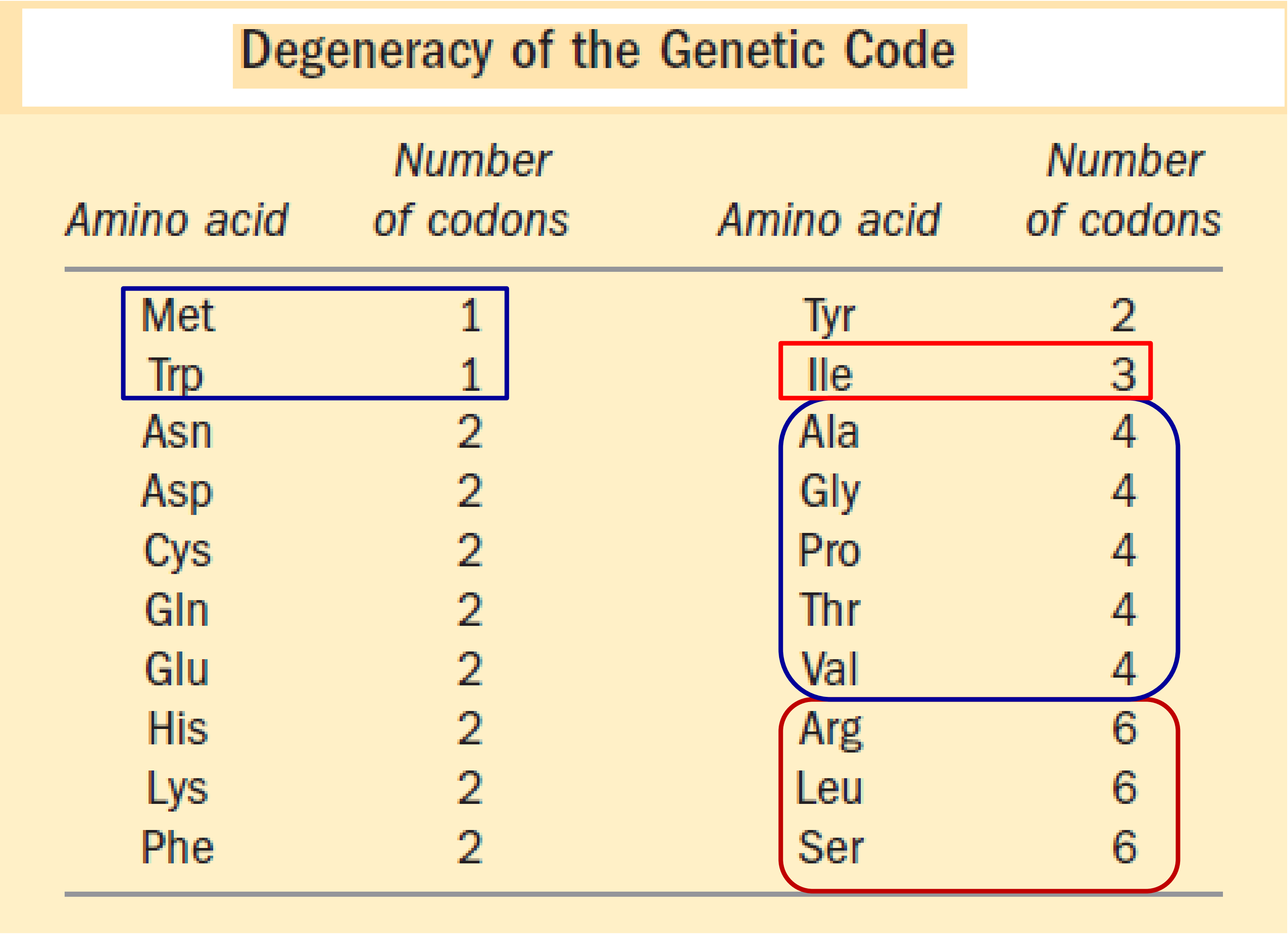


Alcune eccezioni alla regola



Known Deviations from the Universal Genetic Code

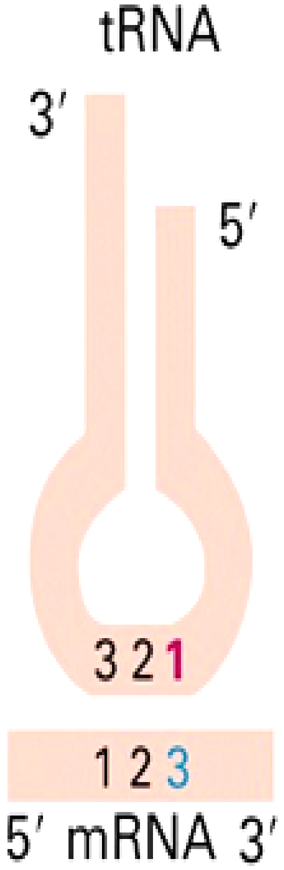
Codon	Universal Code	Unusual Code*	Occurrence
UGA	Stop	Trp	*Mycoplasma*, *Spiroplasma*, mitochondria of many species
CUG	Leu	Thr	Mitochondria in yeasts
UAA, UAG	Stop	Gln	*Acetabularia*, *Tetrahymena*, Paramecium, etc.
UGA	Stop	Cys	*Euplotes*



Degeneracy of the Genetic Code

Amino acid	*Number of codons*	*Amino acid*	*Number of codons*
Met	1	Tyr	2
Trp	1	Ile	3
Asn	2	Ala	4
Asp	2	Gly	4
Cys	2	Pro	4
Gln	2	Thr	4
Glu	2	Val	4
His	2	Arg	6
Lys	2	Leu	6
Phe	2	Ser	6

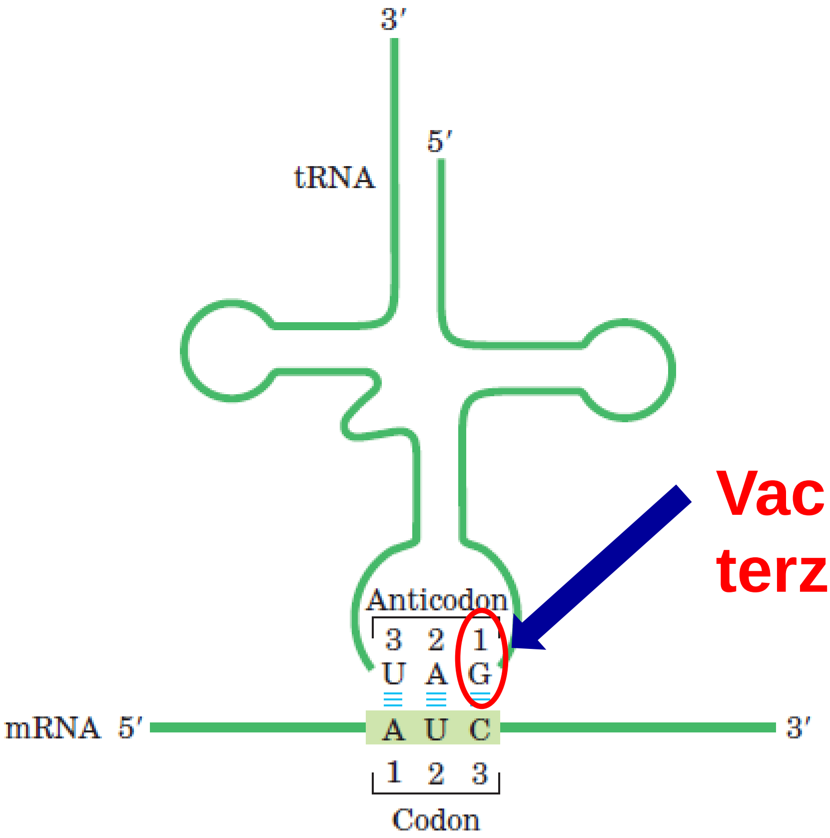
La coppia di basi nella terza posizioni del codone puo’ vacillare



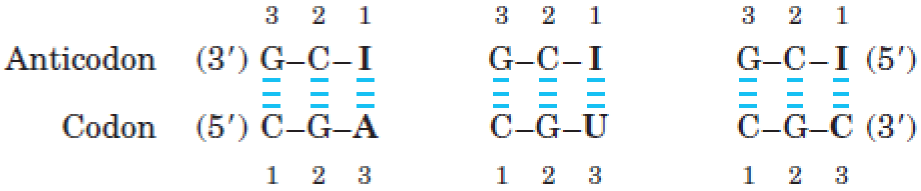
If these bases are in first, or wobble, position of anticodon

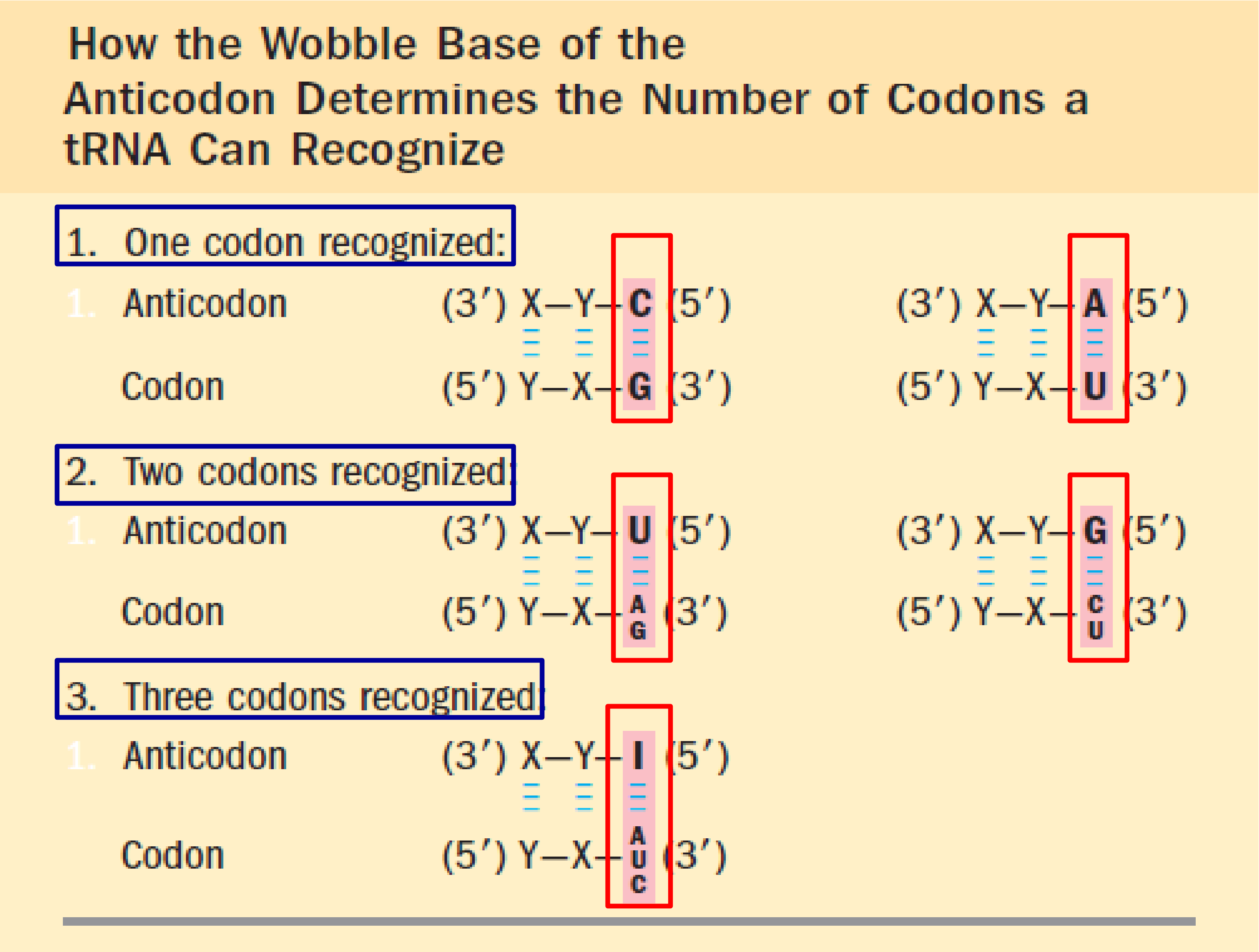
C	A	G	U	I
G	U	C	A	C
		U	G	A
				U

then the tRNA may recognize codons in mRNA having these bases in third position



Vacillamento della terza base





How the Wobble Base of the Anticodon Determines the Number of Codons a tRNA Can Recognize

1. One codon recognized:

Anticodon	(3′) X—Y—**C** (5′)	(3′) X—Y—**A** (5′)
Codon	(5′) Y—X—**G** (3′)	(5′) Y—X—**U** (3′)

2. Two codons recognized:

Anticodon	(3′) X—Y—**U** (5′)	(3′) X—Y—**G** (5′)
Codon	(5′) Y—X—**A** **G** (3′)	(5′) Y—X—**C** **U** (3′)

3. Three codons recognized:

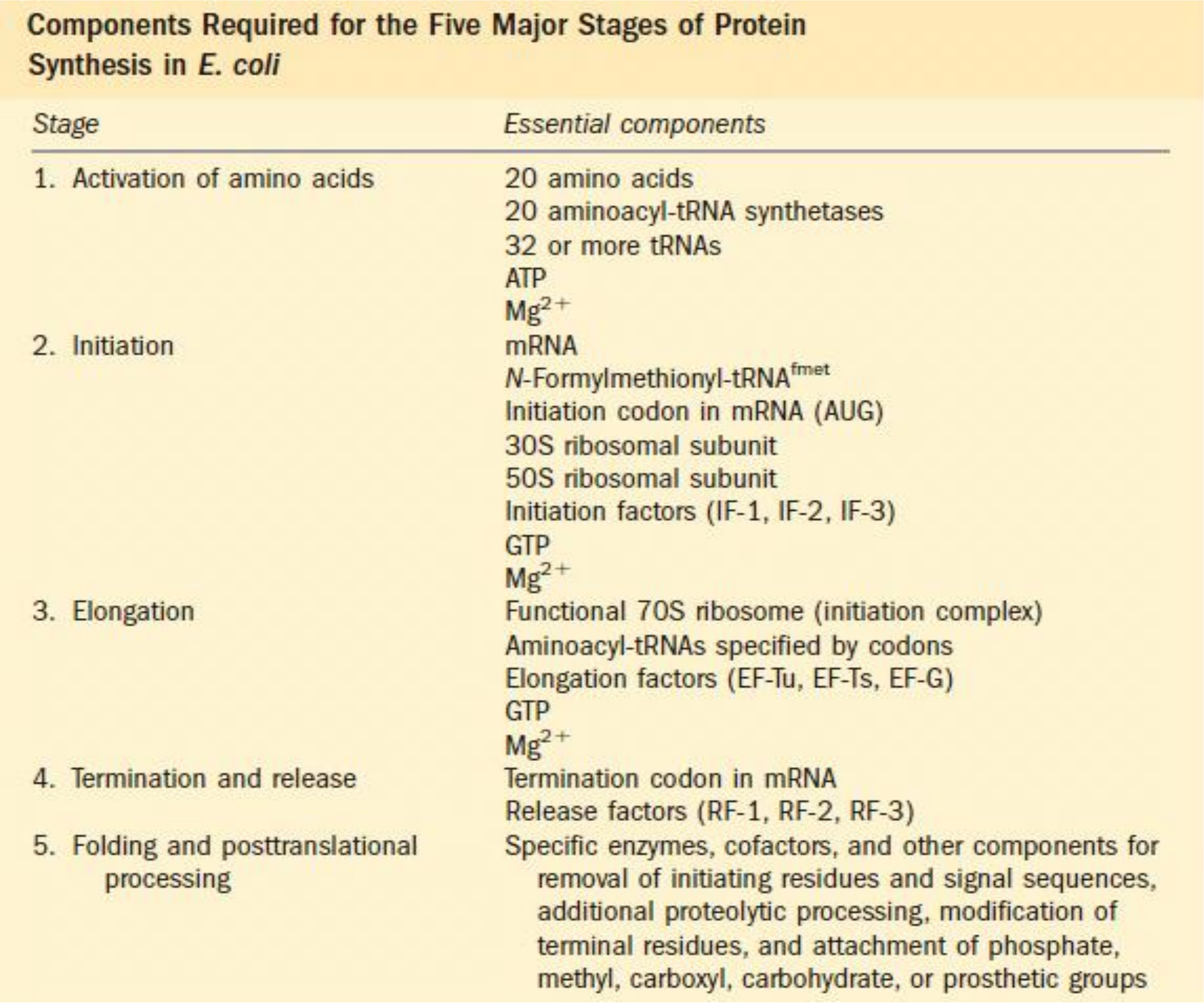
Anticodon	(3′) X—Y—**I** (5′)
Codon	(5′) Y—X—**A** **U** **C** (3′)

Note: X and Y denote bases complementary to and capable of strong Watson-Crick base pairing with X′ and Y′, respectively. Wobble bases—in the 3′ position of codons and 5′ position of anticodons—are shaded in pink.

GCA GCC GCG GCU	AGA AGG CGA CGC CGG CGU	GAC GAU	AAC AAU	UGC UGU	GAA GAG	CAA CAG	GGA GGC GGG GGU	CAC CAU	AUA AUC AUU
Ala	Arg	Asp	Asn	Cys	Glu	Gln	Gly	His	Ile
A	R	D	N	C	E	Q	G	H	I

UUA UUG CUA CUC CUG CUU	AAA AAG	AUG	UUC UUU	CCA CCC CCG CCU	AGC AGU UCA UCC UCG UCU	ACA ACC ACG ACU	UGG	UAC UAU	GUA GUC GUG GUU	UAA UAG UGA
Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val	stop
L	K	M	F	P	S	T	W	Y	V	

Figure 6–50. Molecular Biology of the Cell, 4th Edition.

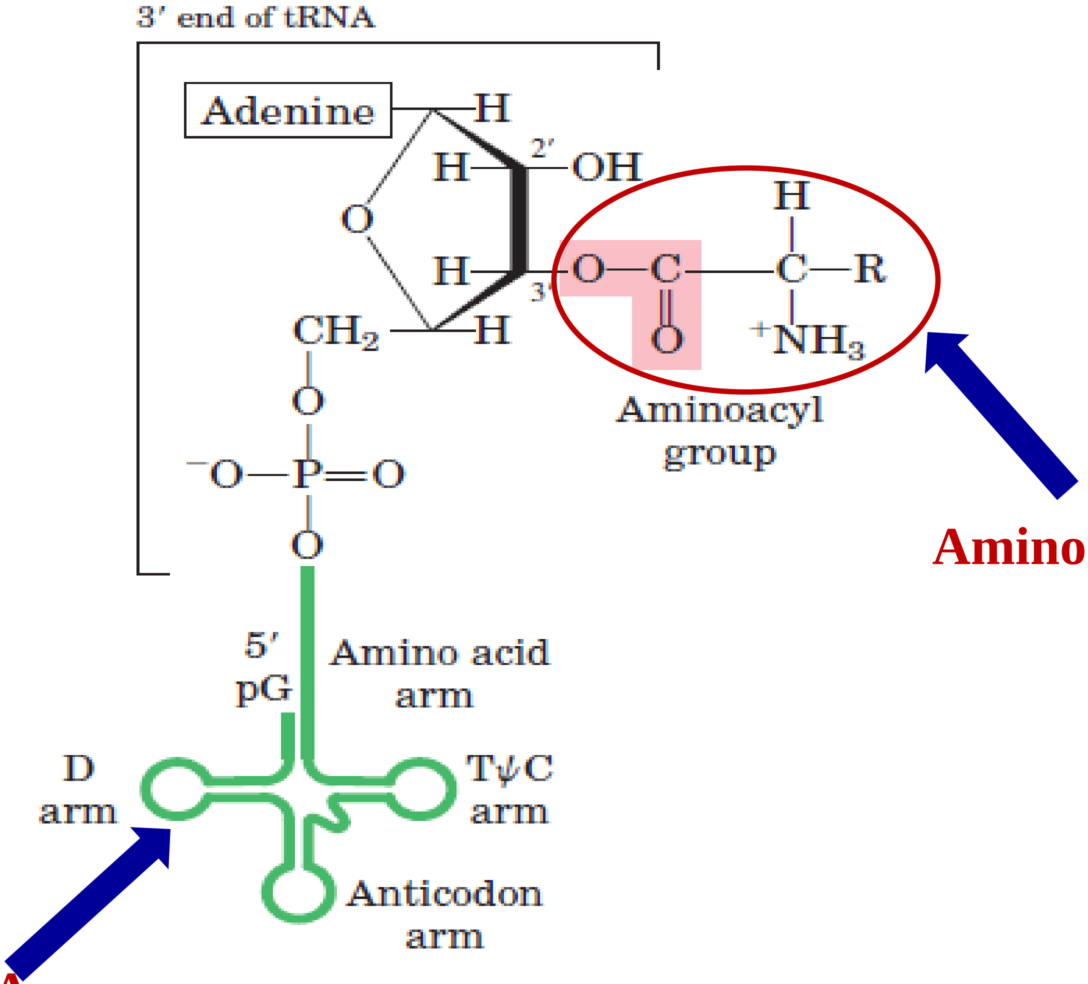


Components Required for the Five Major Stages of Protein Synthesis in *E. coli*

Stage	*Essential components*
1. Activation of amino acids	20 amino acids 20 aminoacyl-tRNA synthetases 32 or more tRNAs ATP Mg^{2+}
2. Initiation	mRNA *N*-Formylmethionyl-tRNA$^{\text{fmet}}$ Initiation codon in mRNA (AUG) 30S ribosomal subunit 50S ribosomal subunit Initiation factors (IF-1, IF-2, IF-3) GTP Mg^{2+}
3. Elongation	Functional 70S ribosome (initiation complex) Aminoacyl-tRNAs specified by codons Elongation factors (EF-Tu, EF-Ts, EF-G) GTP Mg^{2+}
4. Termination and release	Termination codon in mRNA Release factors (RF-1, RF-2, RF-3)
5. Folding and posttranslational processing	Specific enzymes, cofactors, and other components for removal of initiating residues and signal sequences, additional proteolytic processing, modification of terminal residues, and attachment of phosphate, methyl, carboxyl, carbohydrate, or prosthetic groups

Attivazione degli aminoacidi

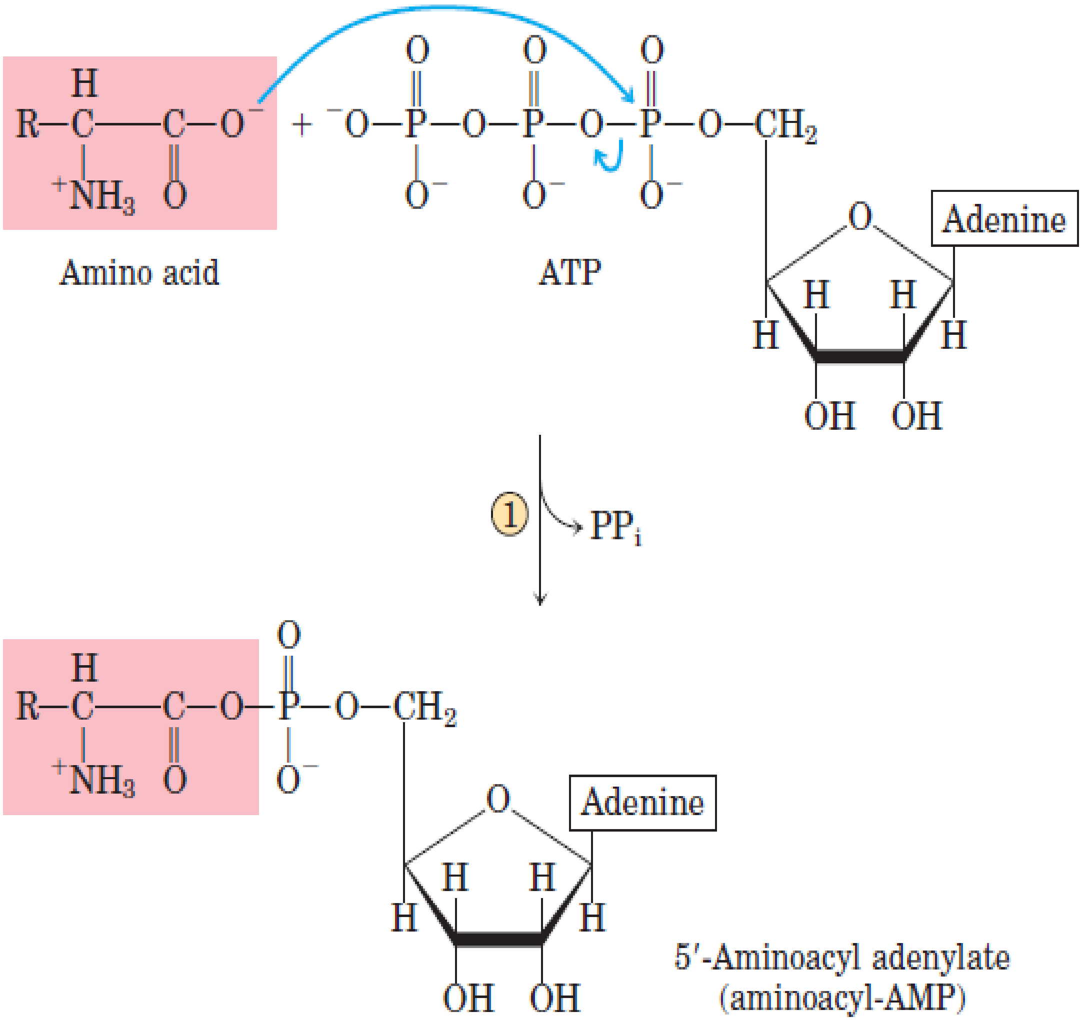
$$\text{Amino acid} + \text{tRNA} + \text{ATP} \xrightleftharpoons{Mg^{2+}} \text{aminoacyl-tRNA} + \text{AMP} + \text{PP}_i$$

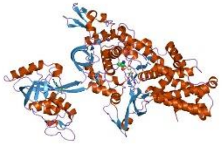


Aminoacido

t-RNA

Aminoacyl t-RNA

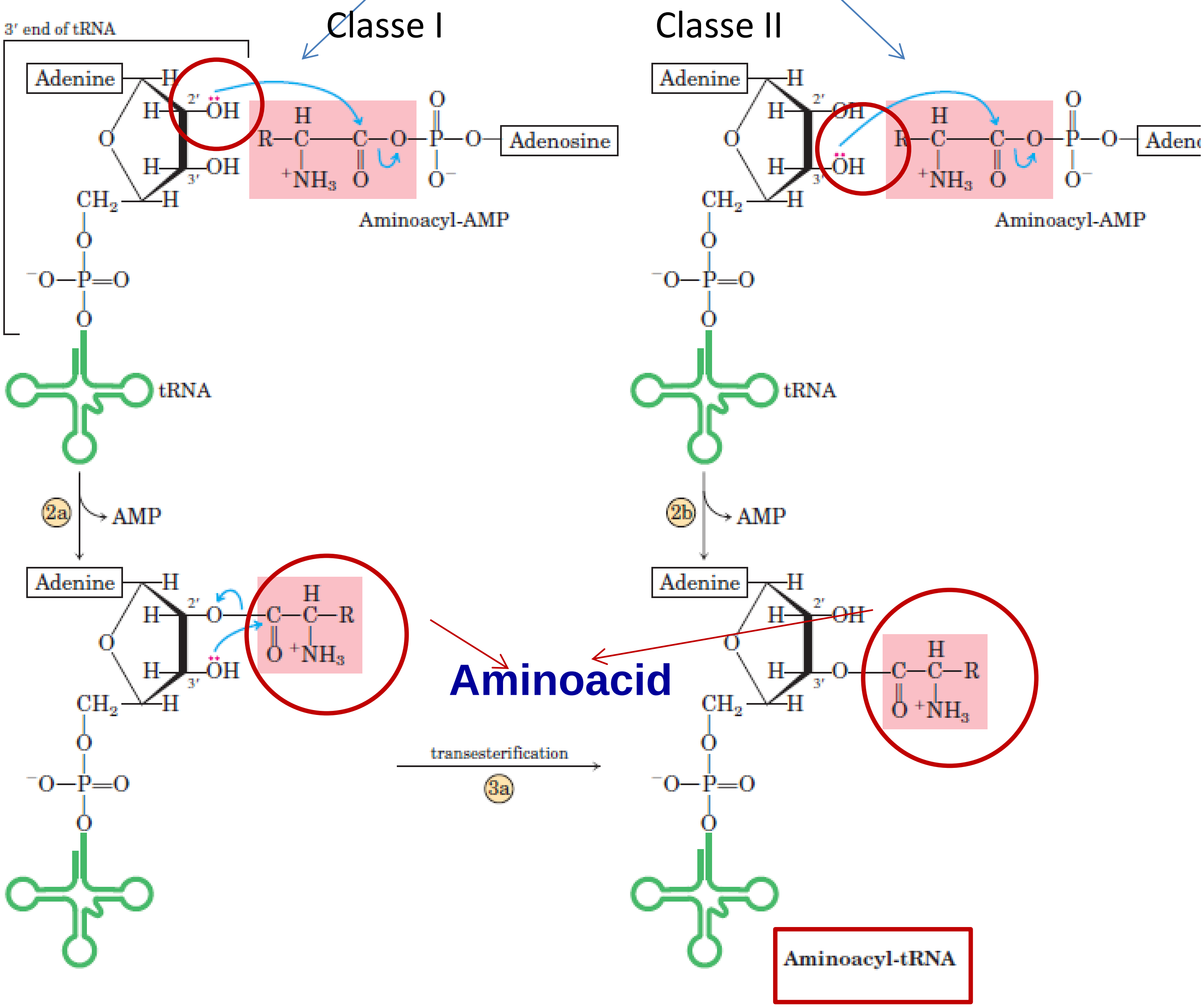

Amino acid
ATP
Adenine
①
PP_i
Adenine
5′-Aminoacyl adenylate
(aminoacyl-AMP)



Uno dei ¬20 aminoacyl-tRNA sintetasi

Classe I

Classe II



Aminoacid

Aminoacyl-tRNA

Amino-acyl tRNA synthetases:

One synthetase for each amino acid a single synthetase may recognize multiple tRNAs or the same amino acid

Two classes of synthetases

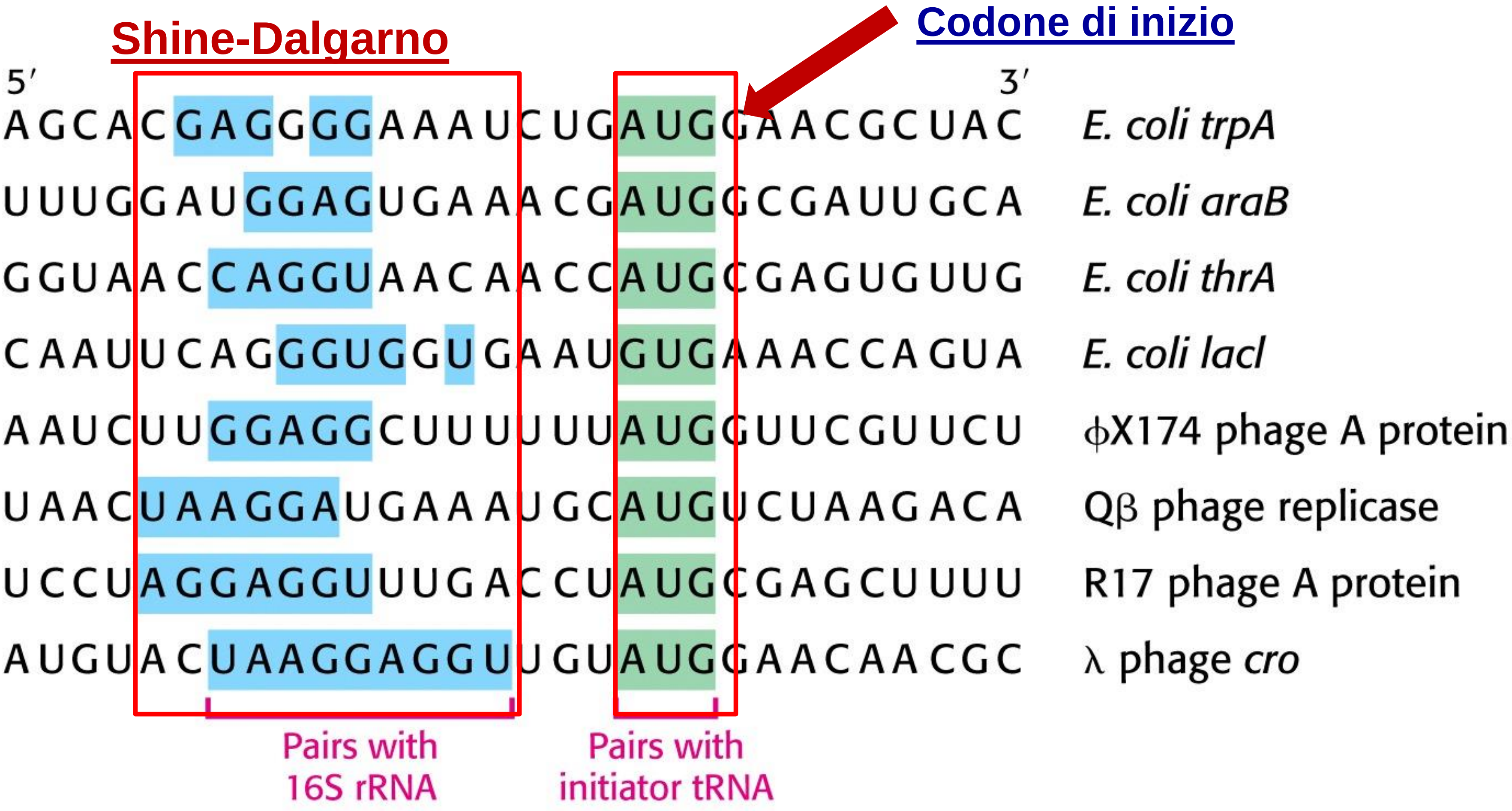
Class I - monomeric, acylates the 2´-OH on the terminal ribose

Arg, Cys , Gln, Glu, Ile, Leu, Met, Trp Tyr, Val

Class II - dimeric, acylates the 3´-OH on the terminal ribose

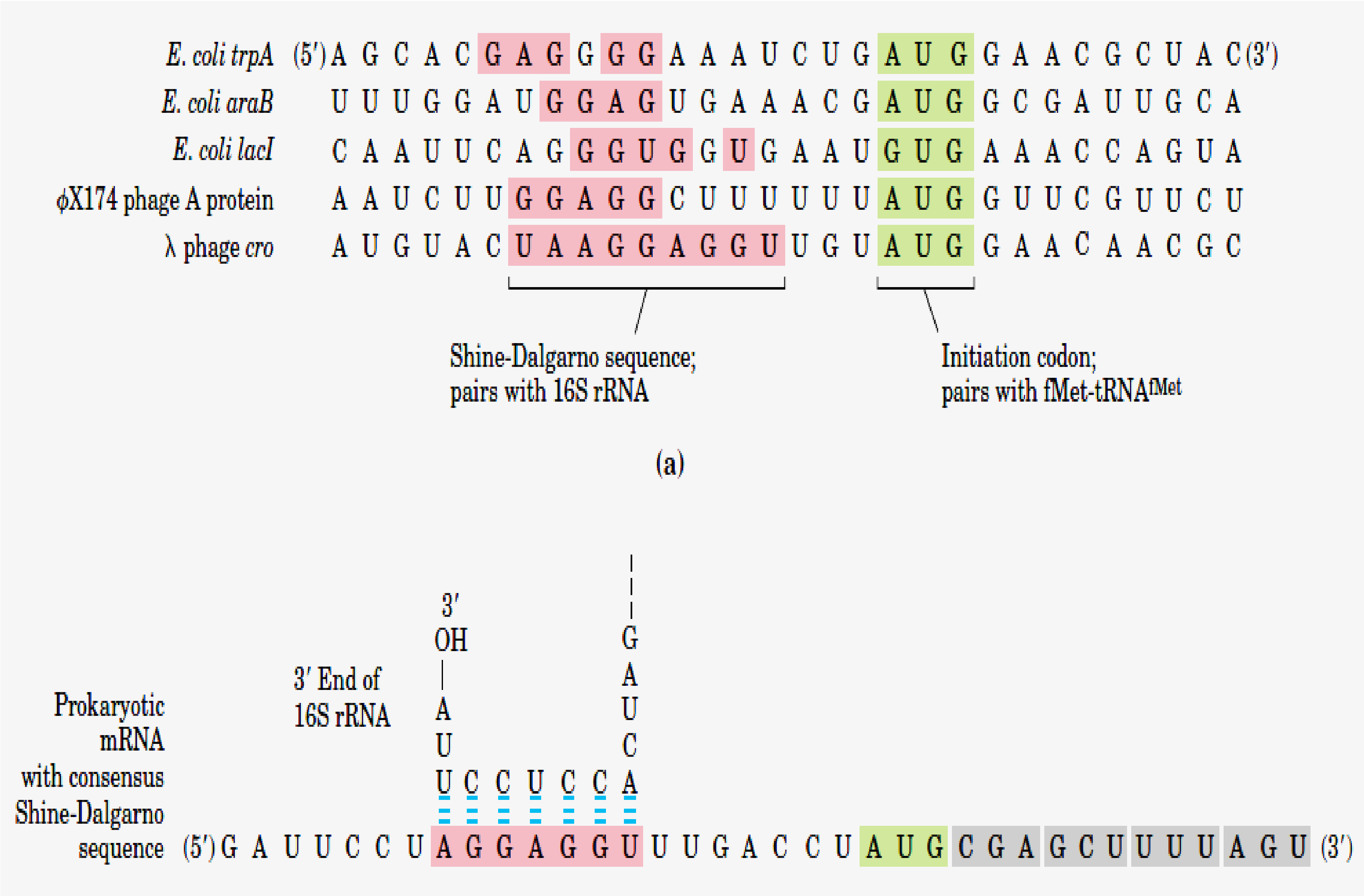
Ala, Asn, Asp, Gly, His, Lys, Phe, Ser, Pro, Thr

La selezione del codone di inizio AUG e’ determinato dai nucleotidi vicini

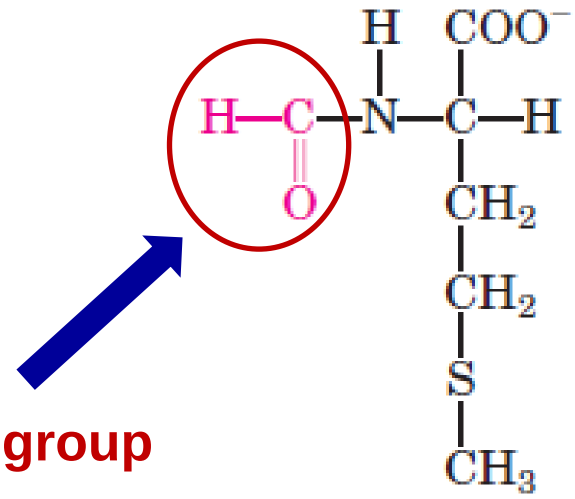


AGCACGAGGGGAAAUCUGAUGGAACGCUAC	*E. coli trpA*
UUUGGAUGGAGUGAAACGAUGGCGAUUGCA	*E. coli araB*
GGUAACCAGGUAACAACCAUGCGAGUGUUG	*E. coli thrA*
CAAUUCAGGGUGGUGAAUGUGAAACCAGUA	*E. coli lacI*
AAUCUUGGAGGCUUUUUUAUGGUUCGUUCU	φX174 phage A protein
UAACUAAGGAUGAAAUGCAUGUCUAAGACA	Qβ phage replicase
UCCUAGGAGGUUUGACCUAUGCGAGCUUUU	R17 phage A protein
AUGUACUAAGGAGGUUGUAUGGAACAACGC	λ phage *cro*

Negli eucarioti: ACCAUGG (Sequenza di Kozak)


E. coli trpA (5′) A G C A C G A G G G G A A A U C U G A U G G A A C G C U A C (3′)
E. coli araB U U U G G A U G G A G U G A A A C G A U G G C G A U U G C A
E. coli lacI C A A U U C A G G G U G G U G A A U G U G A A A C C A G U A
ϕX174 phage A protein A A U C U U G G A G G C U U U U U U A U G G U U C G U U C U
λ phage cro A U G U A C U A A G G A G G U U G U A U G G A A C A A C G C
Shine-Dalgarno sequence; pairs with 16S rRNA
Initiation codon; pairs with fMet-tRNA^{fMet}
(a)
3′ OH
3′ End of 16S rRNA
A U U C C U C C A C U A G
Prokaryotic mRNA with consensus Shine-Dalgarno sequence
(5′) G A U U C C U A G G A G G U U U G A C C U A U G C G A G C U U U U A G U (3′)

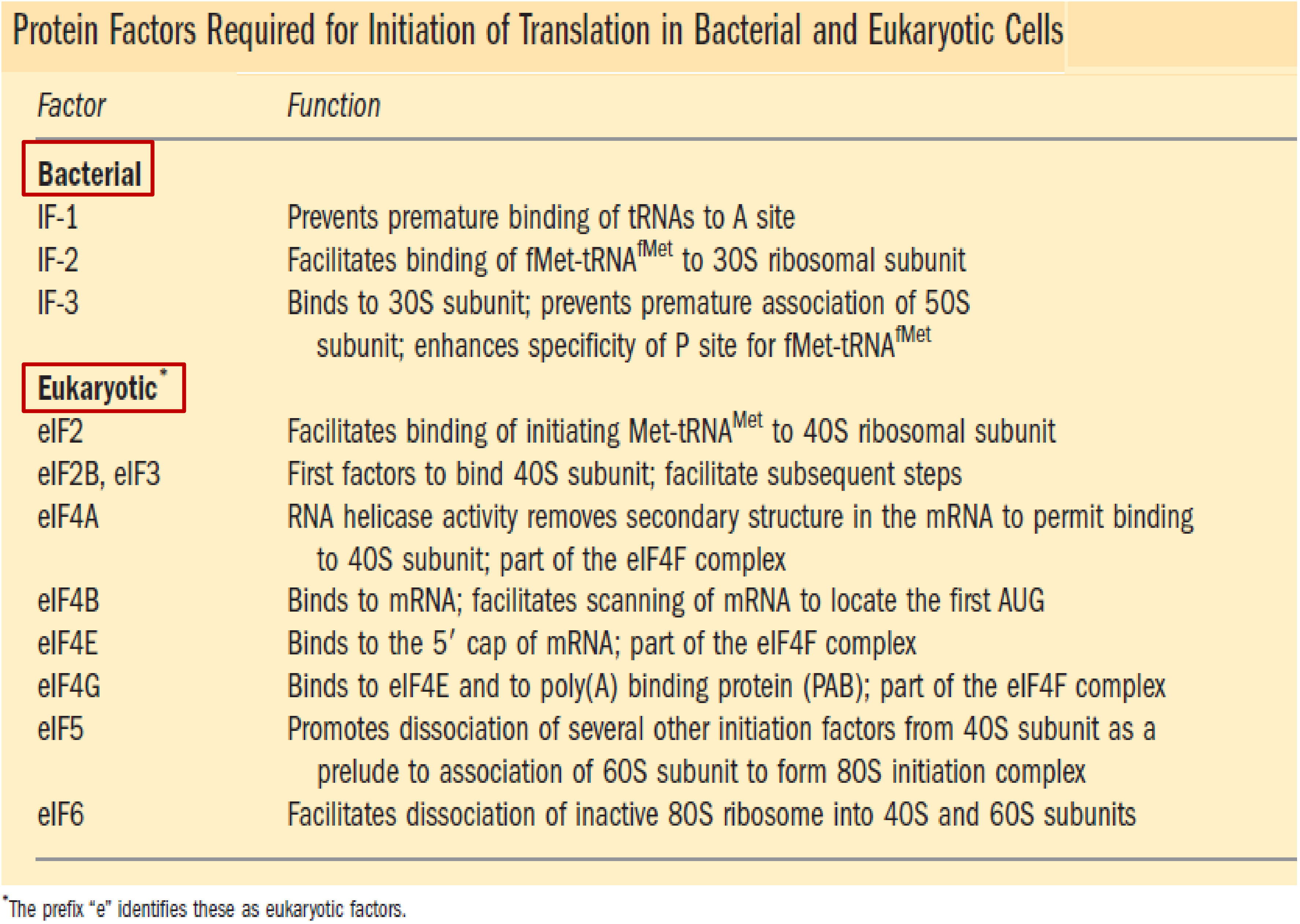
$$\text{Methionine} + \text{tRNA}^{\text{fMet}} + \text{ATP} \longrightarrow \text{Met-tRNA}^{\text{fMet}} + \text{AMP} + \text{PP}_i$$



$$\text{H{-}C({=}O){-}N(H){-}C(H)(COO^-){-}CH_2{-}CH_2{-}S{-}CH_3}$$

formyl group

N-Formylmethionine

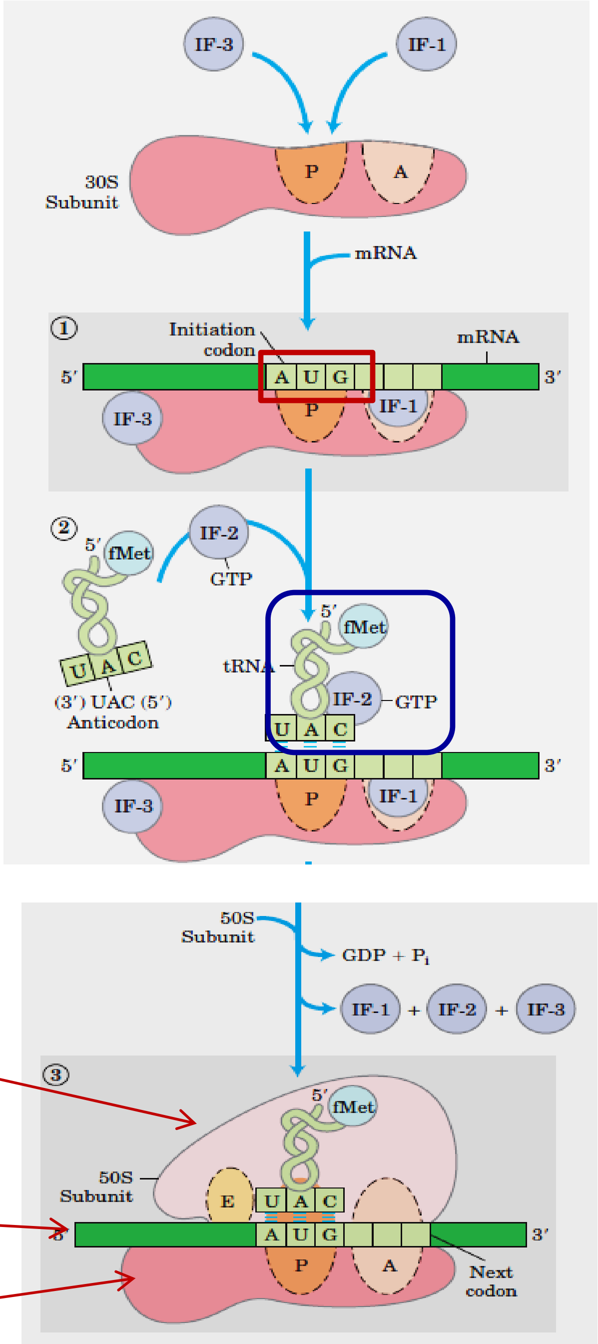


Protein Factors Required for Initiation of Translation in Bacterial and Eukaryotic Cells

Factor	*Function*
Bacterial	
IF-1	Prevents premature binding of tRNAs to A site
IF-2	Facilitates binding of fMet-$\text{tRNA}^{\text{fMet}}$ to 30S ribosomal subunit
IF-3	Binds to 30S subunit; prevents premature association of 50S subunit; enhances specificity of P site for fMet-$\text{tRNA}^{\text{fMet}}$
Eukaryotic[*]	
eIF2	Facilitates binding of initiating Met-tRNA^{Met} to 40S ribosomal subunit
eIF2B, eIF3	First factors to bind 40S subunit; facilitate subsequent steps
eIF4A	RNA helicase activity removes secondary structure in the mRNA to permit binding to 40S subunit; part of the eIF4F complex
eIF4B	Binds to mRNA; facilitates scanning of mRNA to locate the first AUG
eIF4E	Binds to the 5′ cap of mRNA; part of the eIF4F complex
eIF4G	Binds to eIF4E and to poly(A) binding protein (PAB); part of the eIF4F complex
eIF5	Promotes dissociation of several other initiation factors from 40S subunit as a prelude to association of 60S subunit to form 80S initiation complex
eIF6	Facilitates dissociation of inactive 80S ribosome into 40S and 60S subunits

[*] The prefix "e" identifies these as eukaryotic factors.

Iniziazione



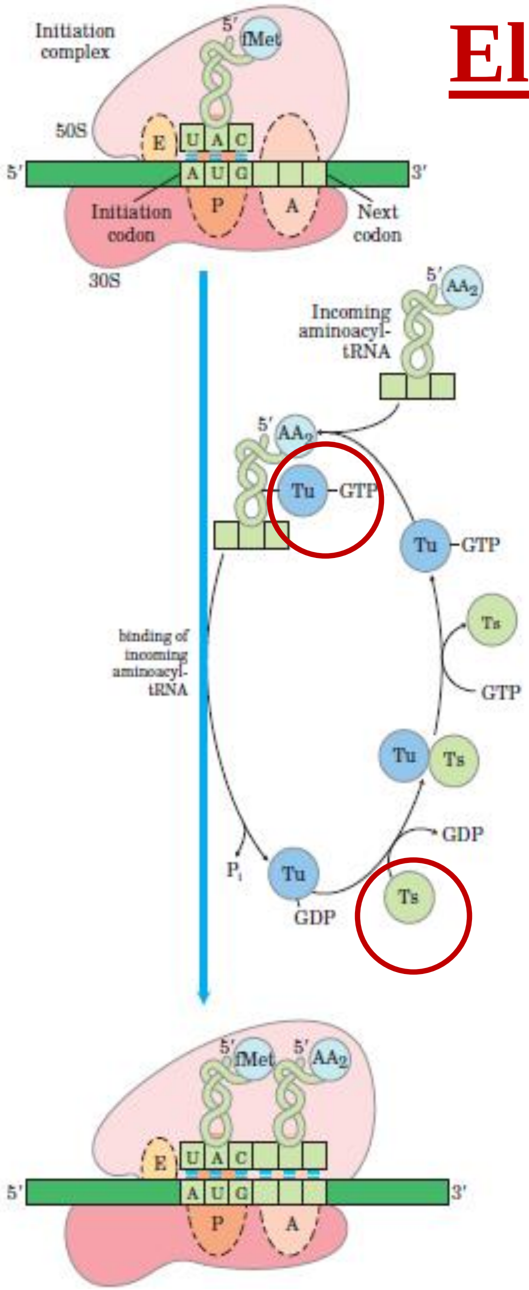
50S Subunita’

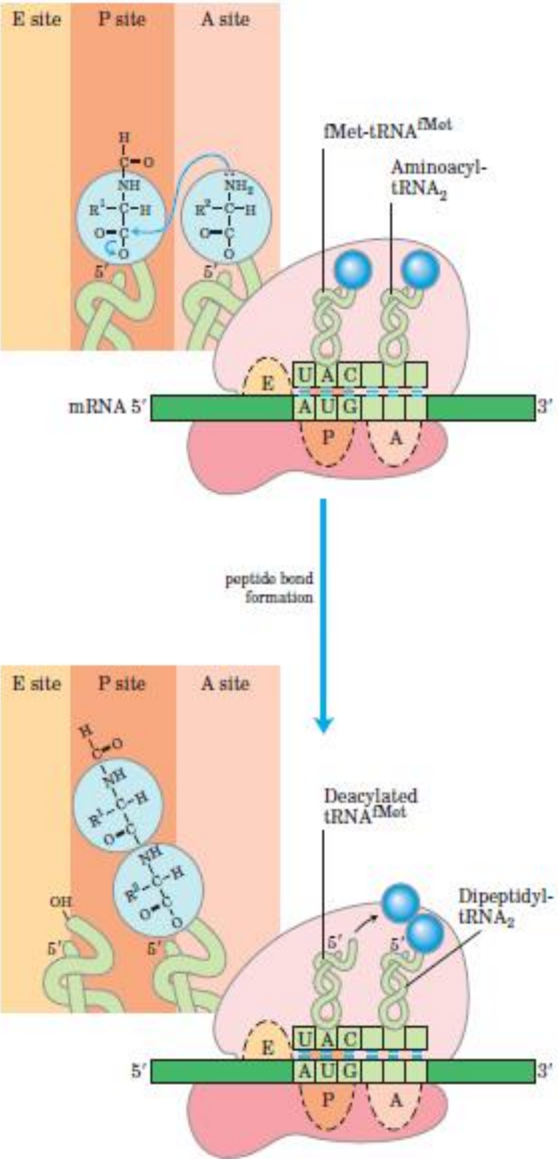
mRNA

30S Subunita’

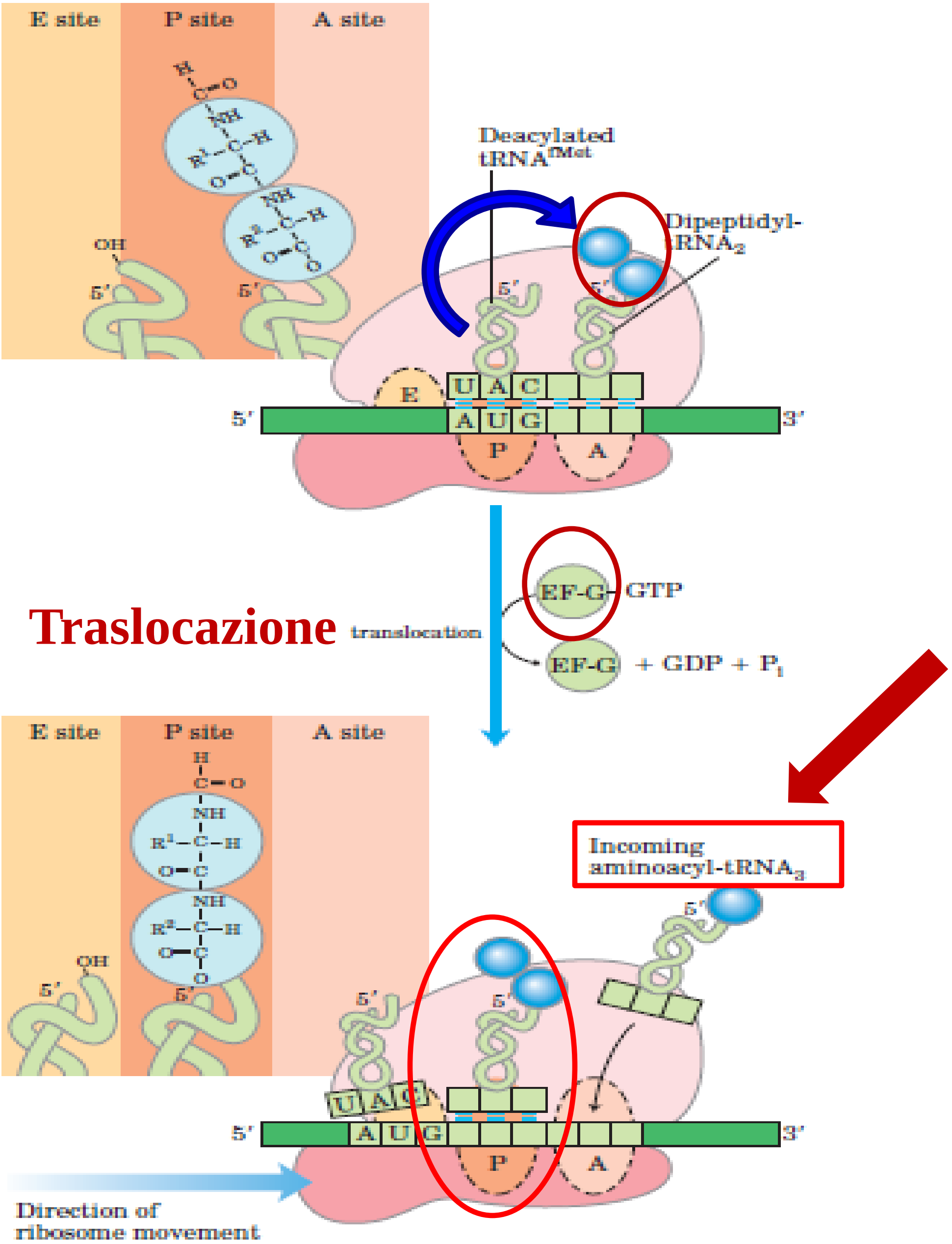
Complesso di Iniziazione 70S

Elongazione

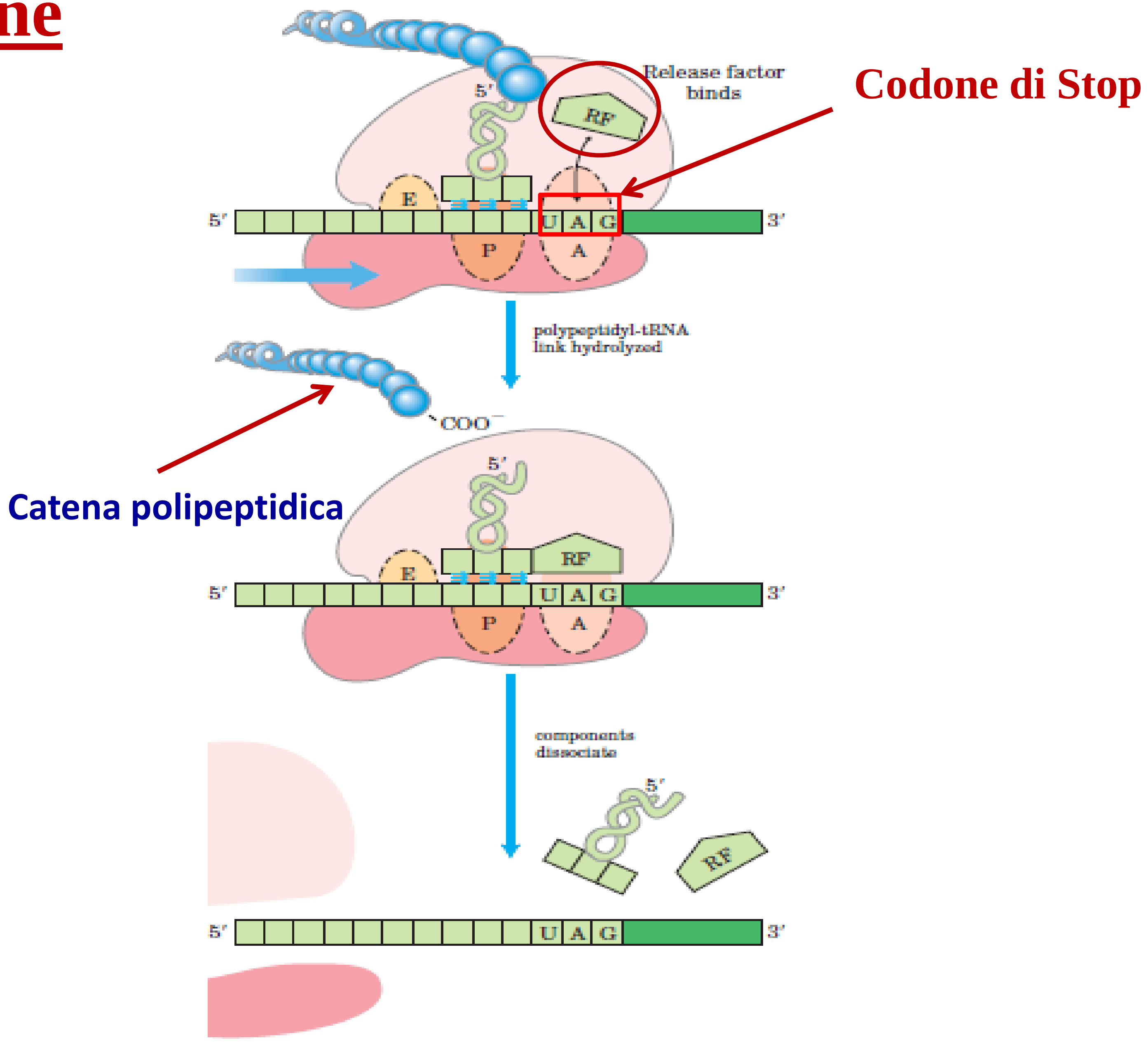




Traslocazione

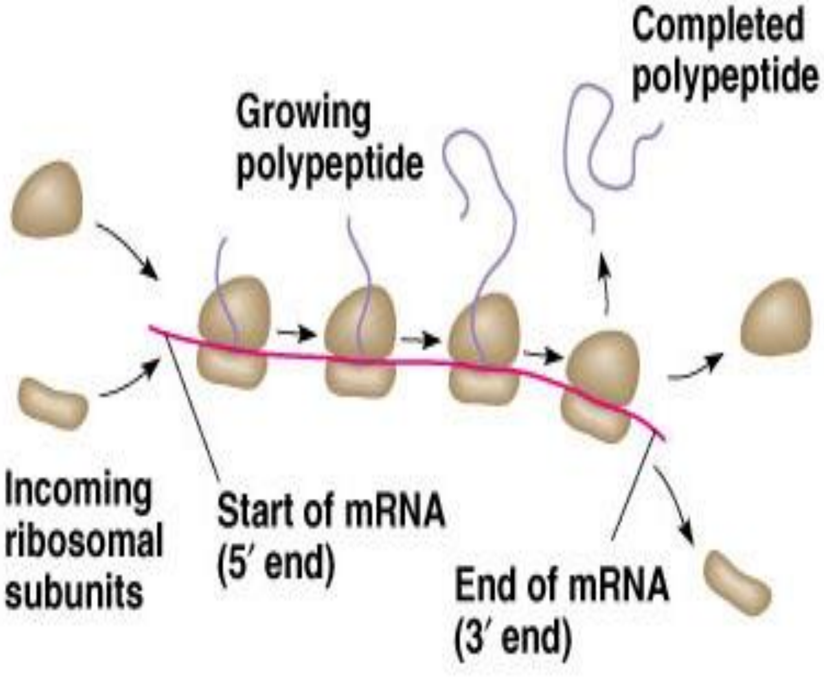


Terminazione

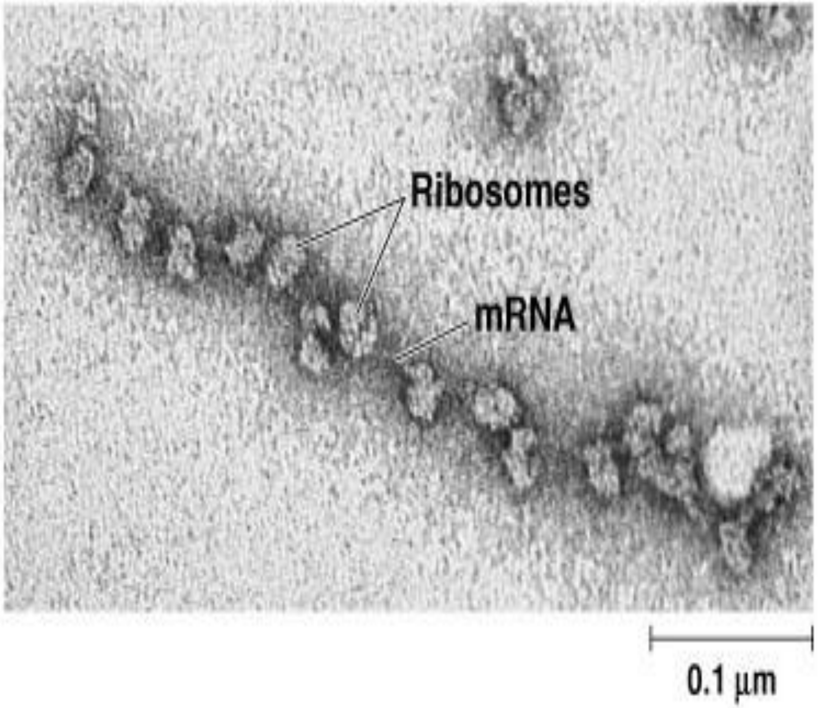


Codone di Stop

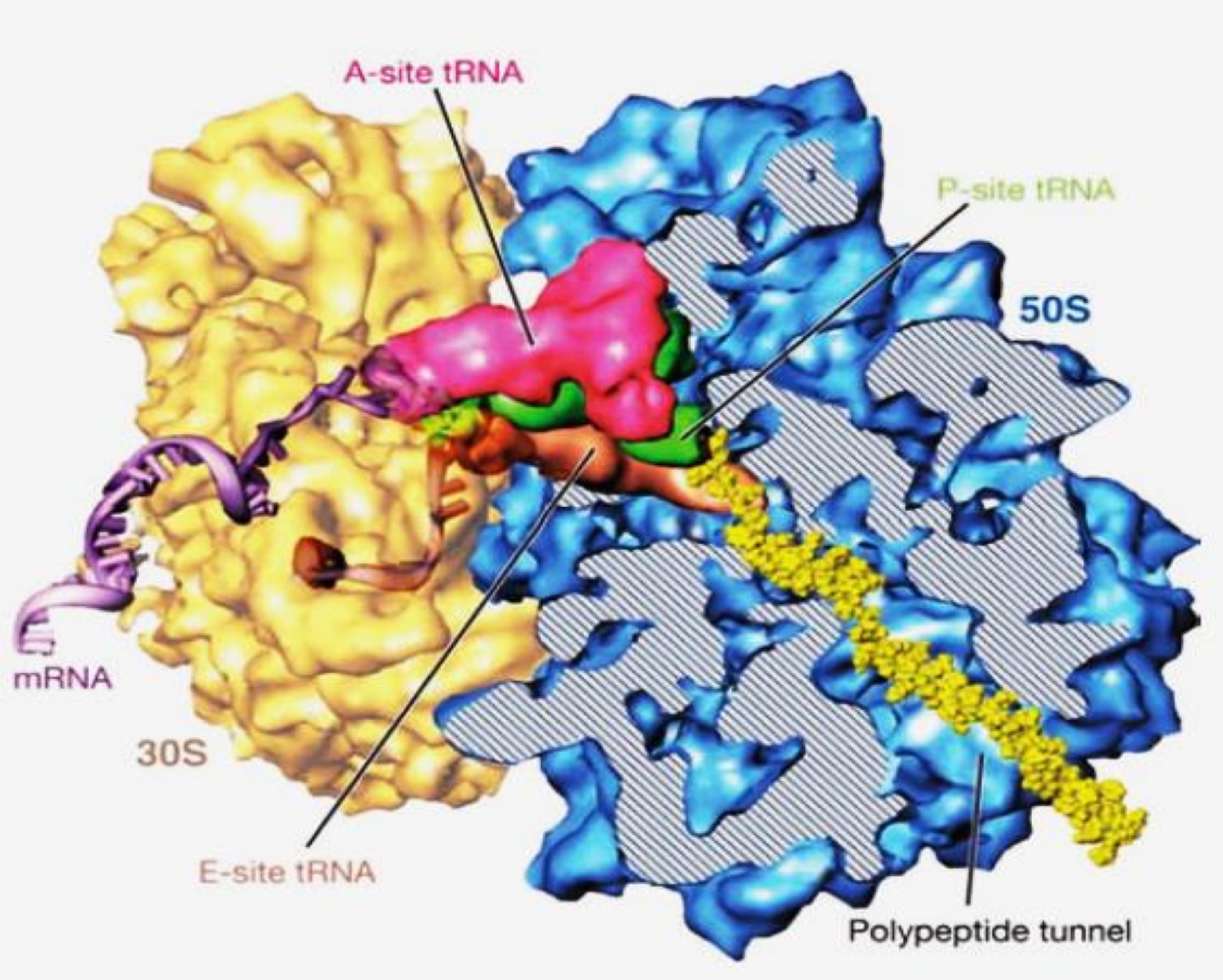
Catena polipeptidica



(a) An mRNA molecule is generally translated simultaneously by several ribosomes in clusters called polyribosomes.



(b) This micrograph shows a large polyribosome in a prokaryotic cell (TEM).


A-site tRNA
P-site tRNA
50S
mRNA
30S
E-site tRNA
Polypeptide tunnel

SINTESI PROTEICA NEGLI EUCARIOTI

La traduzione eucariotica e’ simile al processo procariotico ma e’ molto piu’ complicate (piu fattori coinvolti).

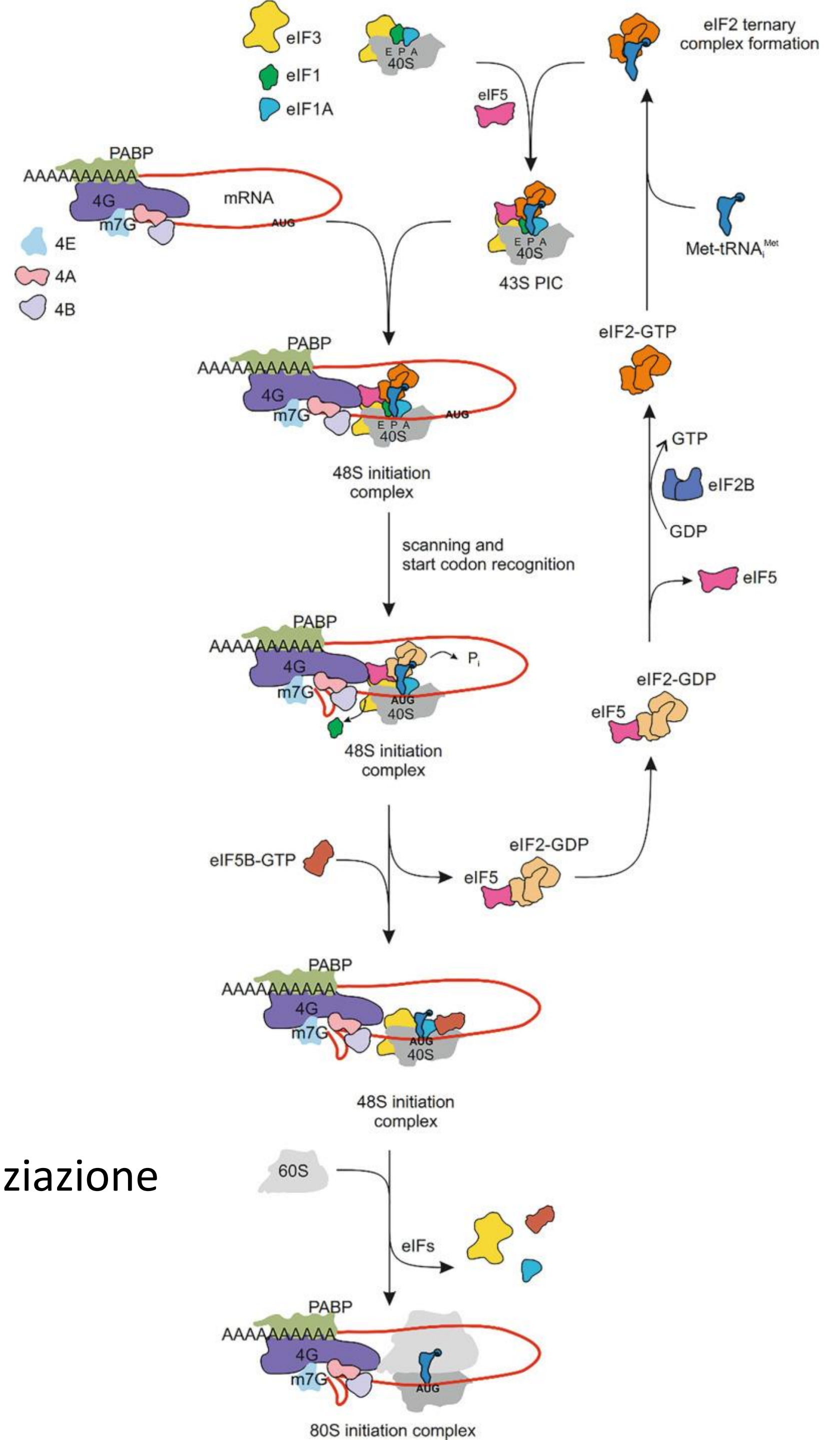
Come nei procarioti avviene in **4 fasi principali**:

1). **Attivazione degli aminoacidi** - Simile

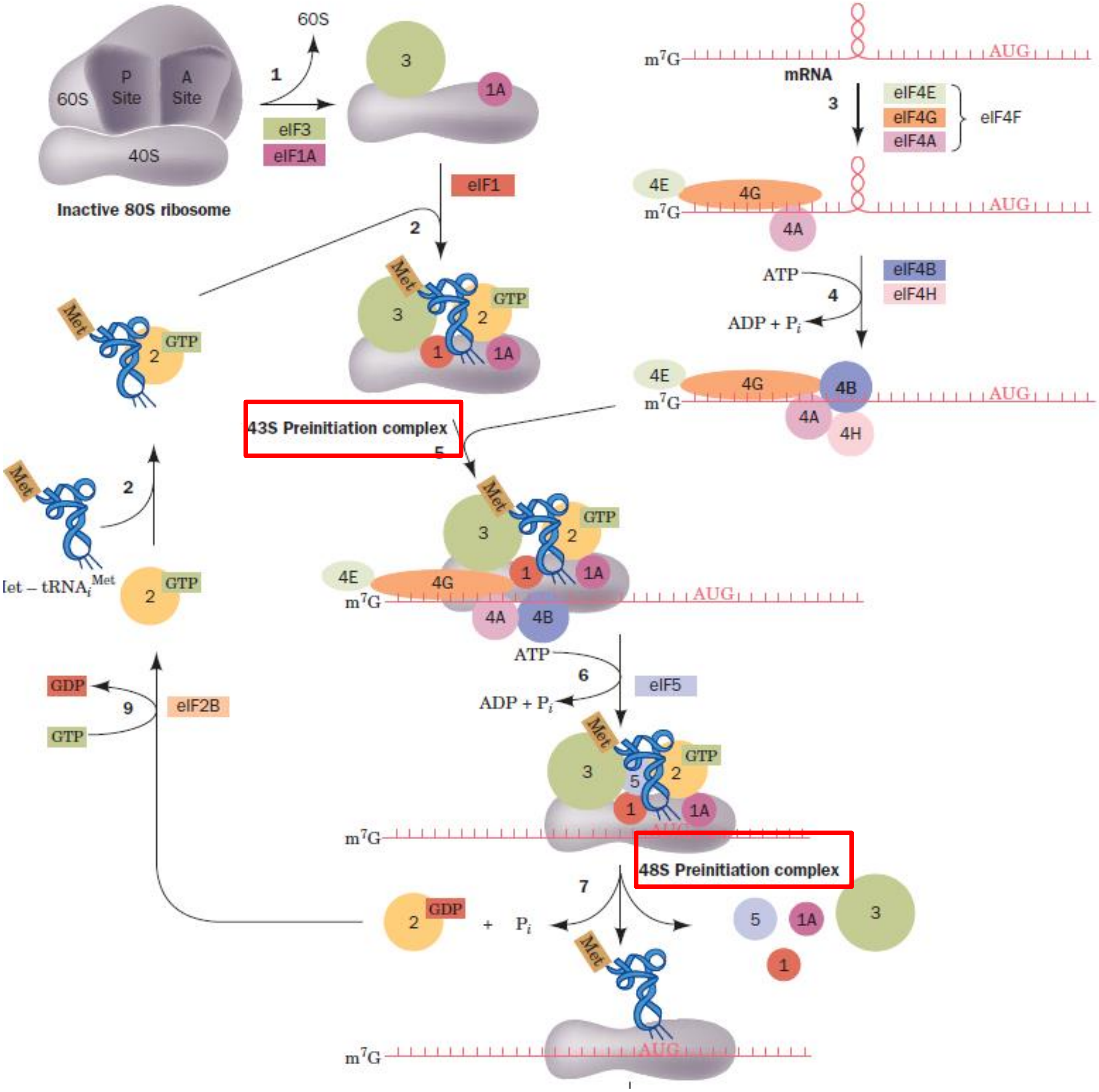
2). **Iniziazione** – Simile ma piu complessa

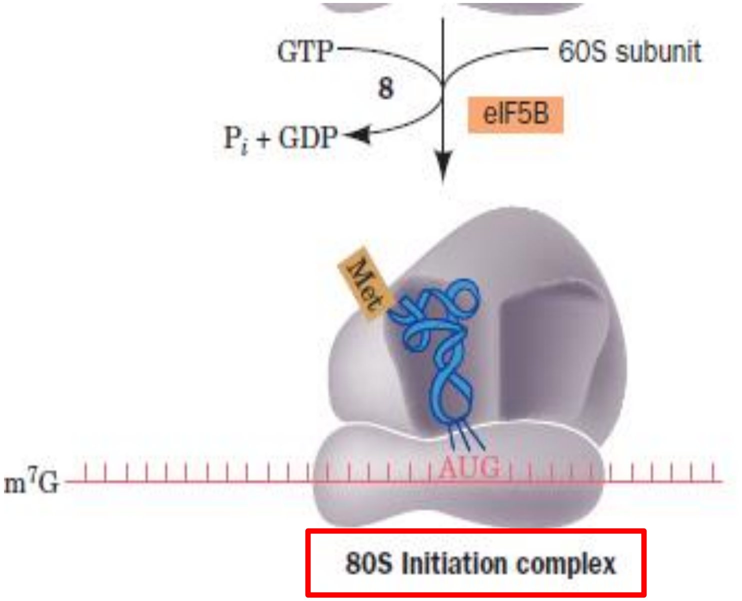
3). **Elongazione** – Simile

4). **Terminazione** - Simile ma piu semplice che nei procarioti, con la necessita’ di solo un **Releasing Factor (RF)**.



PIC: complesso di pre-iniziazione


60S
P Site
A Site
40S
Inactive 80S ribosome
1
60S
eIF3
eIF1A
3
1A
eIF1
2
m7G
AUG
mRNA
3
eIF4E
eIF4G
eIF4A
eIF4F
4E
4G
4A
ATP
4
ADP + Pi
eIF4B
eIF4H
4B
4H
Met
GTP
2
1
43S Preinitiation complex
5
let – tRNAiMet
ATP
6
ADP + Pi
eIF5
GDP
9
GTP
eIF2B
48S Preinitiation complex
7
GDP
+ Pi
5
1A
3
1



L'elongazione e la **fase di terminazione negli eucarioti e' molto simile a quella dei procarioti eccetto che solo un eRF (o un) TF e' sufficiente per mediare la terminazione**

Although methionine (Met) is the first amino acid incorporated into any new protein, it is not always the first amino acid in mature proteins—in many proteins, methionine is removed after translation. In fact, if a large number of proteins are sequenced and compared with their known gene sequences, methionine (or formylmethionine) occurs at the N-terminus of all of them. However, not all amino acids are equally likely to occur second in the chain, and the second amino acid influences whether the initial methionine is enzymatically removed. For example, many proteins begin with methionine followed by alanine. In both prokaryotes and eukaryotes, these proteins have the methionine removed, so that alanine becomes the N-terminal amino acid (Table 1). However, if the second amino acid is lysine, which is also frequently the case, methionine is not removed (at least in the sample proteins that have been studied thus far). These proteins therefore begin with methionine followed by lysine (Flinta *et al.*, 1986).

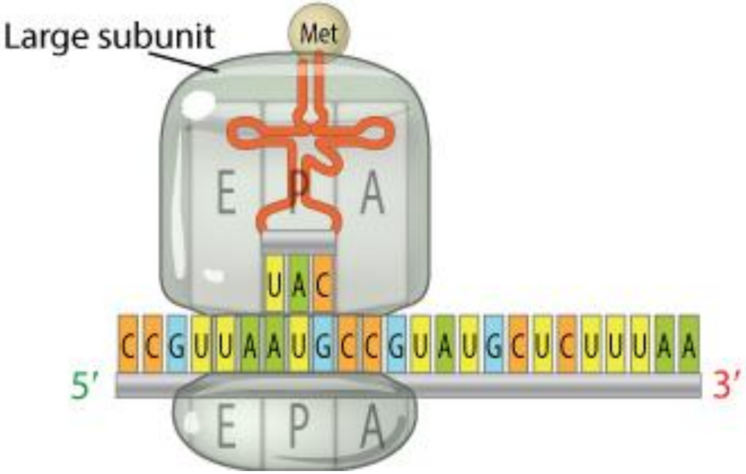
Table 1 shows the N-terminal sequences of proteins in prokaryotes and eukaryotes, based on a sample of 170 prokaryotic and 120 eukaryotic proteins (Flinta *et al.*, 1986). In the table, M represents methionine, A represents alanine, K represents lysine, S represents serine, and T represents threonine.

Table 1: N-Terminal Sequences of Proteins

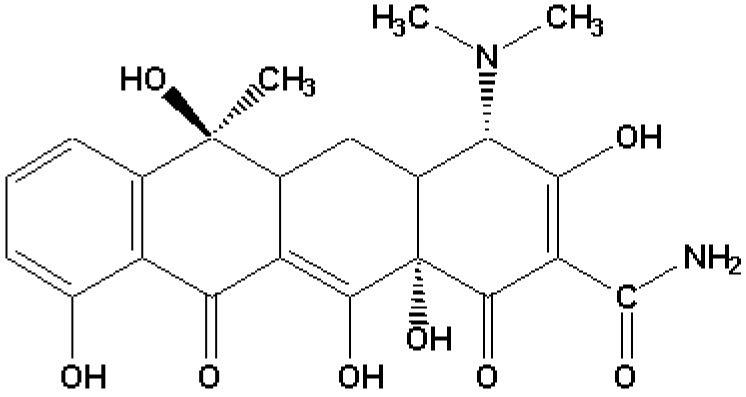
N-Terminal Sequence	**Percent of Prokaryotic Proteins with This Sequence**	**Percent of Eukaryotic Proteins with This Sequence**
MA*	28.24%	19.17%
MK**	10.59%	2.50%
MS*	9.41%	11.67%
MT*	7.65%	6.67%

* Methionine was removed in all of these proteins

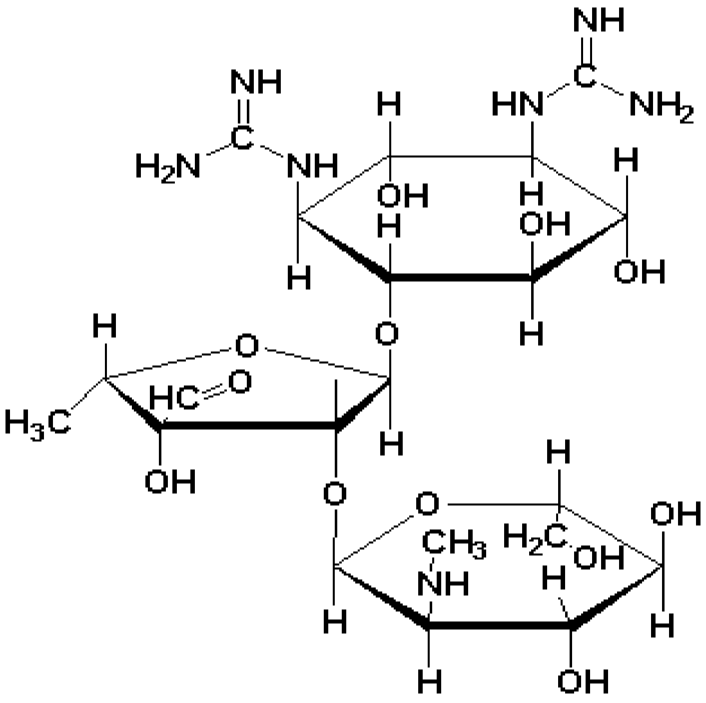
** Methionine was not removed from any of these proteins



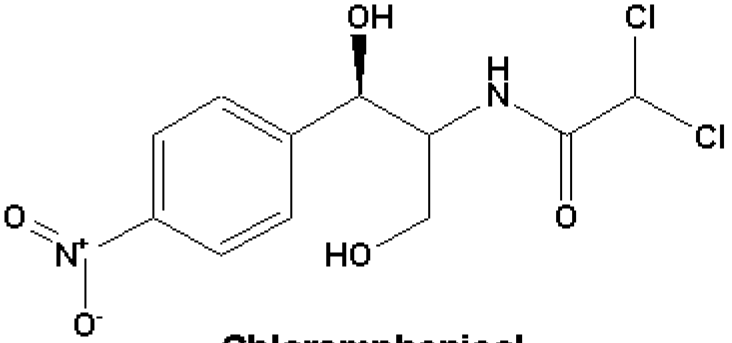
Inibitori



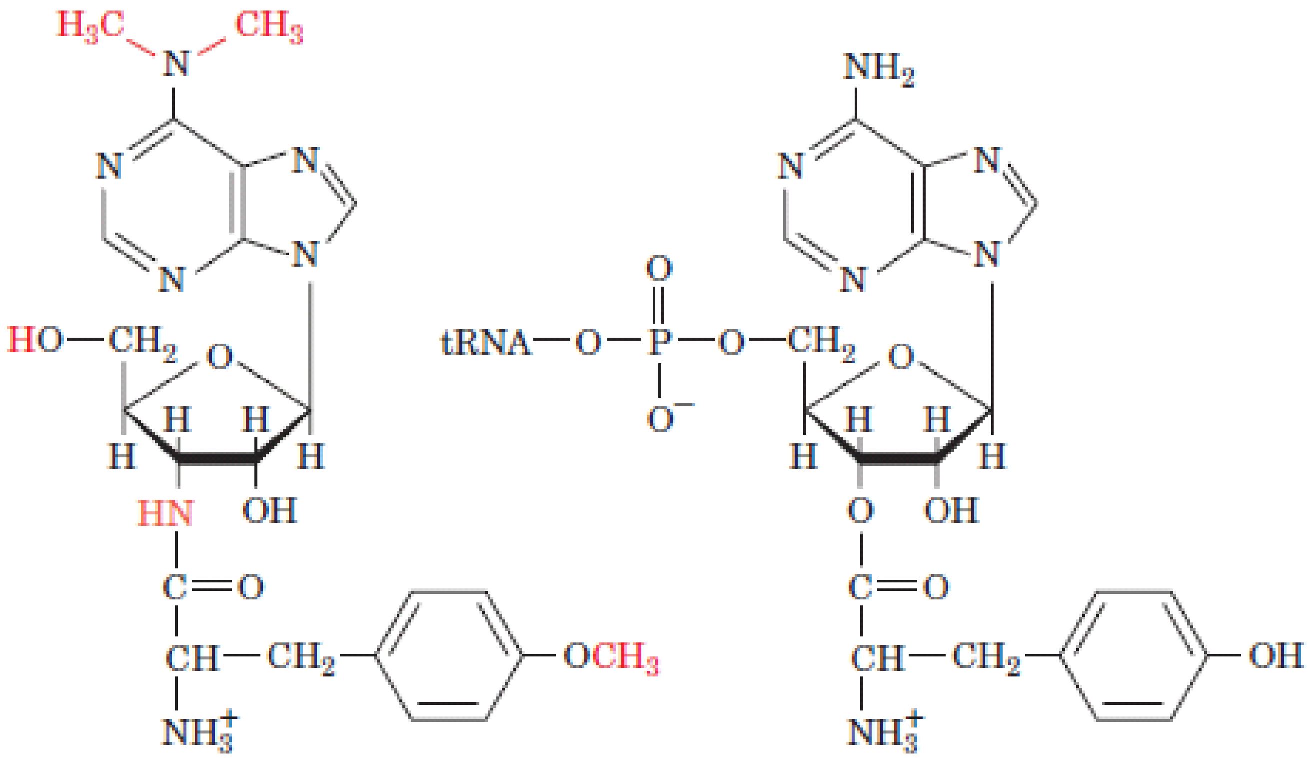
Tetracycline



Streptomycin



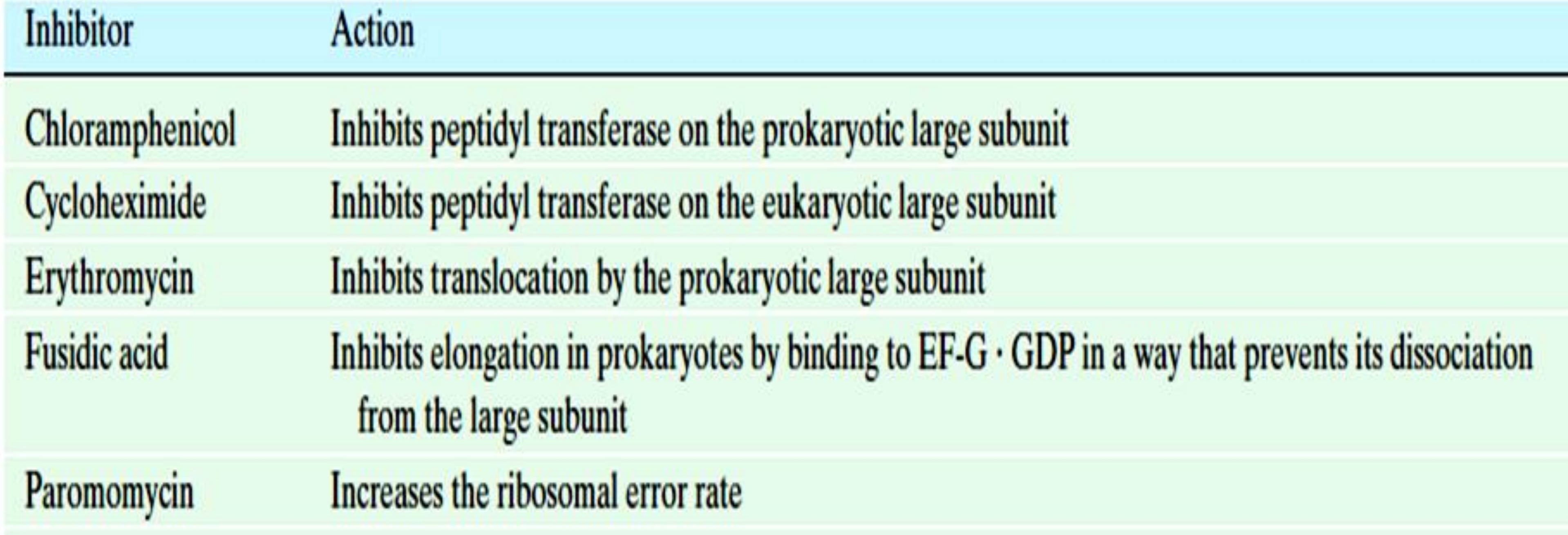
Chloramphenicol



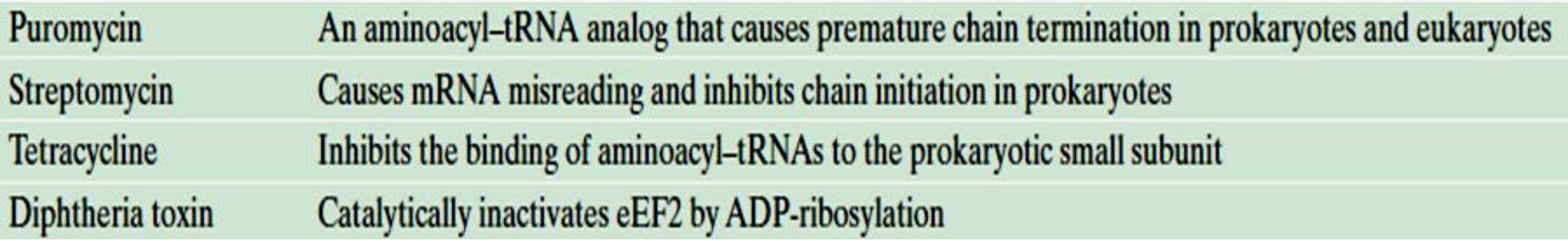
Puromycin

Tyrosyl–tRNA

Molti composti inibiscono la traduzione in procarioti ed eucarioti



Inhibitor	Action
Chloramphenicol	Inhibits peptidyl transferase on the prokaryotic large subunit
Cycloheximide	Inhibits peptidyl transferase on the eukaryotic large subunit
Erythromycin	Inhibits translocation by the prokaryotic large subunit
Fusidic acid	Inhibits elongation in prokaryotes by binding to EF-G · GDP in a way that prevents its dissociation from the large subunit
Paromomycin	Increases the ribosomal error rate



Puromycin	An aminoacyl–tRNA analog that causes premature chain termination in prokaryotes and eukaryotes
Streptomycin	Causes mRNA misreading and inhibits chain initiation in prokaryotes
Tetracycline	Inhibits the binding of aminoacyl–tRNAs to the prokaryotic small subunit
Diphtheria toxin	Catalytically inactivates eEF2 by ADP-ribosylation

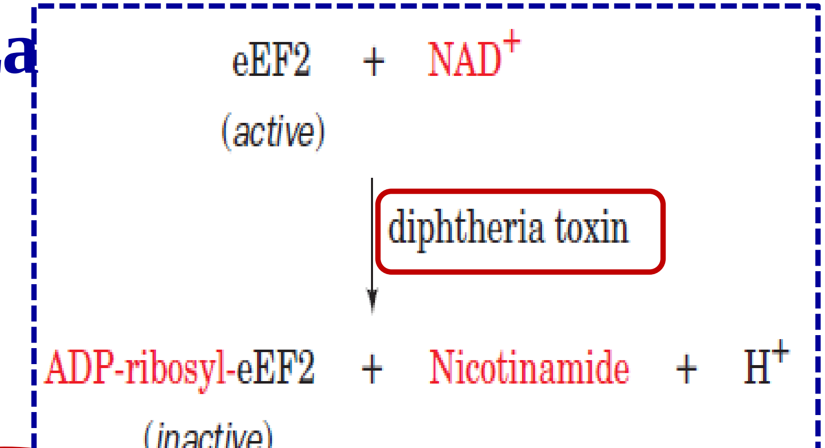
Tossina della difterite

- **La difterite e' una malattia risultante dall'infezione del batterio *Corynebacterium diphtheriae*.**

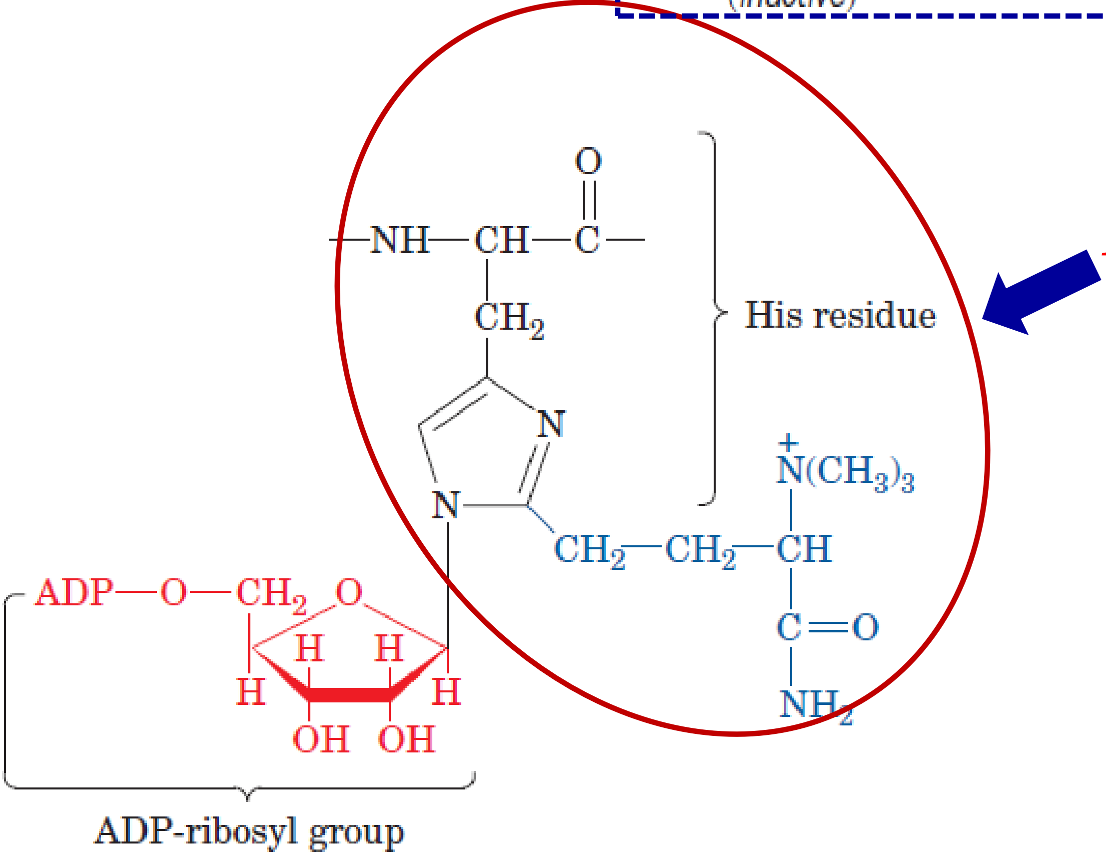
- ***Diphtheria toxin (DT)*, e' una proteina monomerica con 535 residui aminoacidici, responsabili per gli effetti letali della malattia.**

- ***Diphtheria toxin* inattiva specificamente il *factor di elungazione eucariotico eEF2*, quindi inibendo la sintesi proteica eucariotica.**

La tossina della difterite catalizza la ribosilazione dell’ADP di una *diphthamide* (un’istidina modificata) di *eEF2*, inattivandolo.



$$\underset{(active)}{\text{eEF2}} + \text{NAD}^+ \xrightarrow{\boxed{\text{diphtheria toxin}}} \underset{(inactive)}{\text{ADP-ribosyl-eEF2}} + \text{Nicotinamide} + \text{H}^+$$



Dipthamide

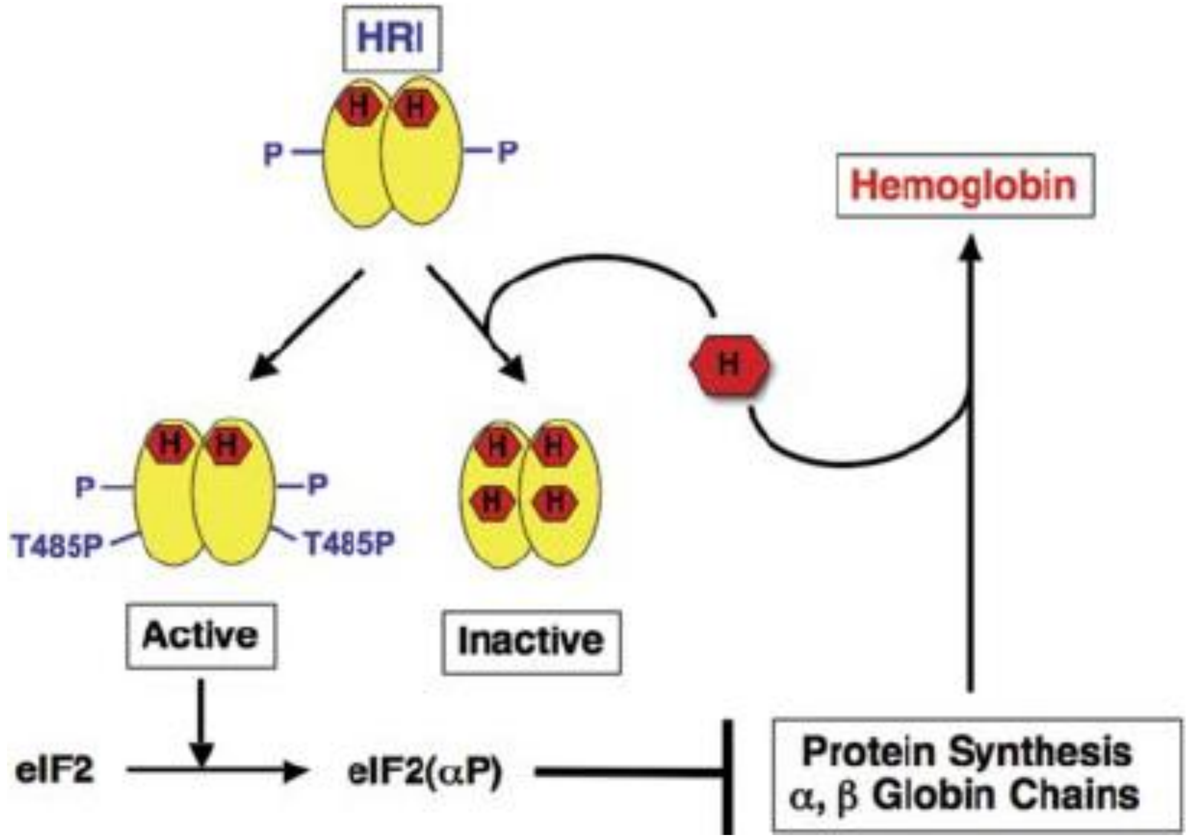
ADP-Ribosylated diphthamide

Regolazione della sintesi di Eme & Emoglobina

- Negli eucarioti la disponibilita’ di eme controlla la sintesi di emoglobina.

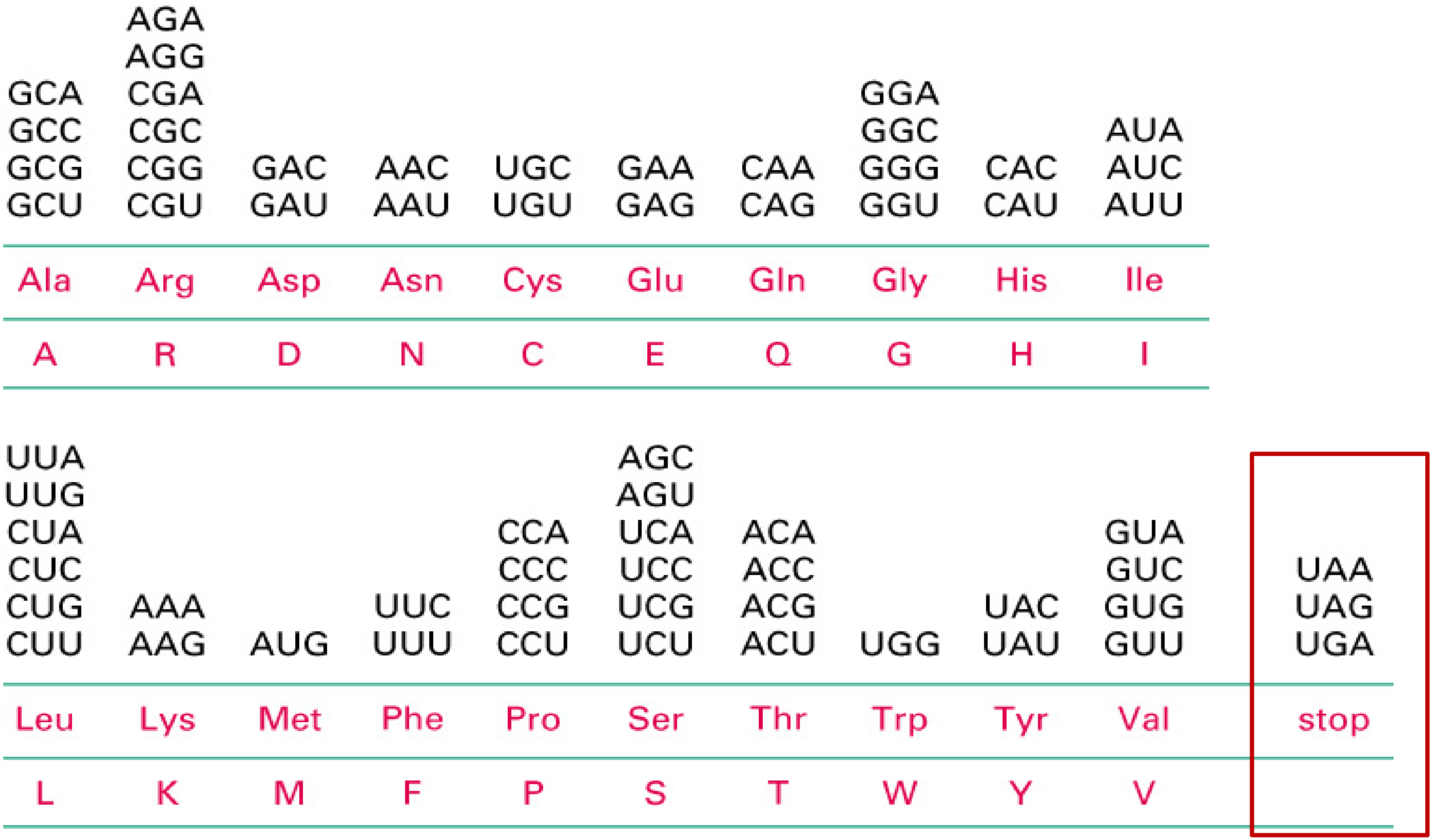
- Alti livelli di *eIF2* e GTP sono essenziali per la traduzione dell’emoglobina.

- Una eIF2 kinasi chiamata heme-regulated inhibit (HRI) oppure heme-controlled repressor (HCR) regola la sintesi di emoglobina sulla base della presenza o assenza di eme.



HRI balances heme and globin synthesis by sensing intracellular heme concentrations.
During the synthesis of hemoglobin, one molecule of heme is incorporated into each globin chain.
When heme concentration is high, heme binds to the second heme-binding domain
of HRI and keeps HRI in inactive state, thereby permitting globin protein synthesis and the
formation of stable hemoglobin. In heme deficiency, HRI is activated by autophosphorylation.
Activated HRI phosphorylates eIF2 ⎵ and inhibits globin protein synthesis by the mechanism illustrated.
HRI, therefore, acts as a feedback inhibitor of globin synthesis to ensure no globin is translated
in excess of the heme available for assembly of stable hemoglobin.

Evoluzione del codice genetico



GCA GCC GCG GCU	AGA AGG CGA CGC CGG CGU	GAC GAU	AAC AAU	UGC UGU	GAA GAG	CAA CAG	GGA GGC GGG GGU	CAC CAU	AUA AUC AUU	
Ala	Arg	Asp	Asn	Cys	Glu	Gln	Gly	His	Ile	
A	R	D	N	C	E	Q	G	H	I	
UUA UUG CUA CUC CUG CUU	AAA AAG	AUG	UUC UUU	CCA CCC CCG CCU	AGC AGU UCA UCC UCG UCU	ACA ACC ACG ACU	UGG	UAC UAU	GUA GUC GUG GUU	UAA UAG UGA
Leu	Lys	Met	Phe	Pro	Ser	Thr	Trp	Tyr	Val	stop
L	K	M	F	P	S	T	W	Y	V	

Figure 6–50. Molecular Biology of the Cell, 4th Edition.

Evoluzione del codice genetico

Tre principali teorie:

- **Teoria adattativa:** l’evoluzione ha reso ottimale la corrispondenza codone-aminoacido. Improbabile che spieghi tutto visti gli ottimi locali di fitness, la varieta’ di organismi, e la possibilita’ di regolare la disponibilita’ dei vari tRNA.

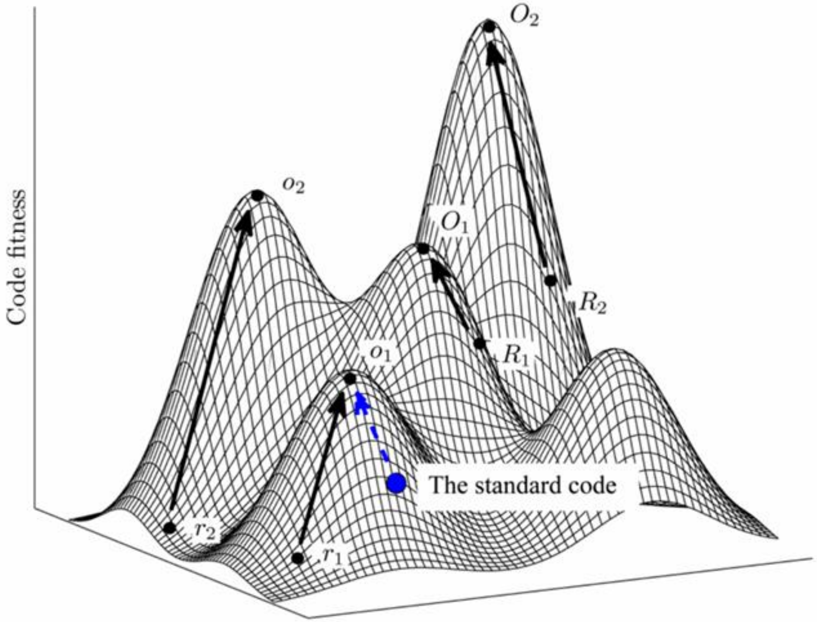


Fig. 3.
Evolution of codes in a rugged fitness landscape (a cartoon illustration).
r_1, $r_2 \in \mathbf{r}$: random codes with the same block structure as the standard code
o_1, $o_2 \in \mathbf{o}$: codes obtained from $r_{1,\ r2} \in \mathbf{r}$ after optimization
R_1, $R_2 \in \mathbf{R}$: random codes with fitness values greater than the fitness of the standard code
O_1, $O_2 \in \mathbf{O}$: codes obtained from R_1, $R_2 \in \mathbf{R}$ after optimization
The figure is modified from (86).

Evoluzione del codice genetico

Tre principali teorie:

- Teoria adattativa: l’evoluzione ha reso ottimale la corrispondenza codone-aminoacido. Improbabile che spieghi tutto visti gli ottimi locali di fitness, la varieta’ di organismi, e la possibilita’ di regolare la disponibilita’ dei vari tRNA.
- **Teoria stereochimica:** corrispondenze biochimiche tra aminoacidic e codoni/anticodoni (Gamow, 1954). Non molto supportata.
- **Teoria coevolutiva**: teorizza il fatto che in una prima fase prebiotica esistessero meno aminoacidi. In seguito, questi aminoacidic si sarebbero specializzati e quindi “sottocodoni” (differenti per la terza base) sarebbero stati adottati per aminoacidi affini derivati o con pathway biosintetici comuni. La terza fase e’ quella delle mofiche post-traduzionali e degli aminoacidic modificati.

Teoria coevolutiva

Published in final edited form as:
IUBMB Life. 2009 February ; 61(2): 99–111. doi:10.1002/iub.146.

Origin and evolution of the genetic code: the universal enigma

Eugene V. Koonin[*] and **Artem S. Novozhilov**
National Center for Biotechnology Information, National Library of Medicine, National Institutes of Health, Bethesda, MD 20894

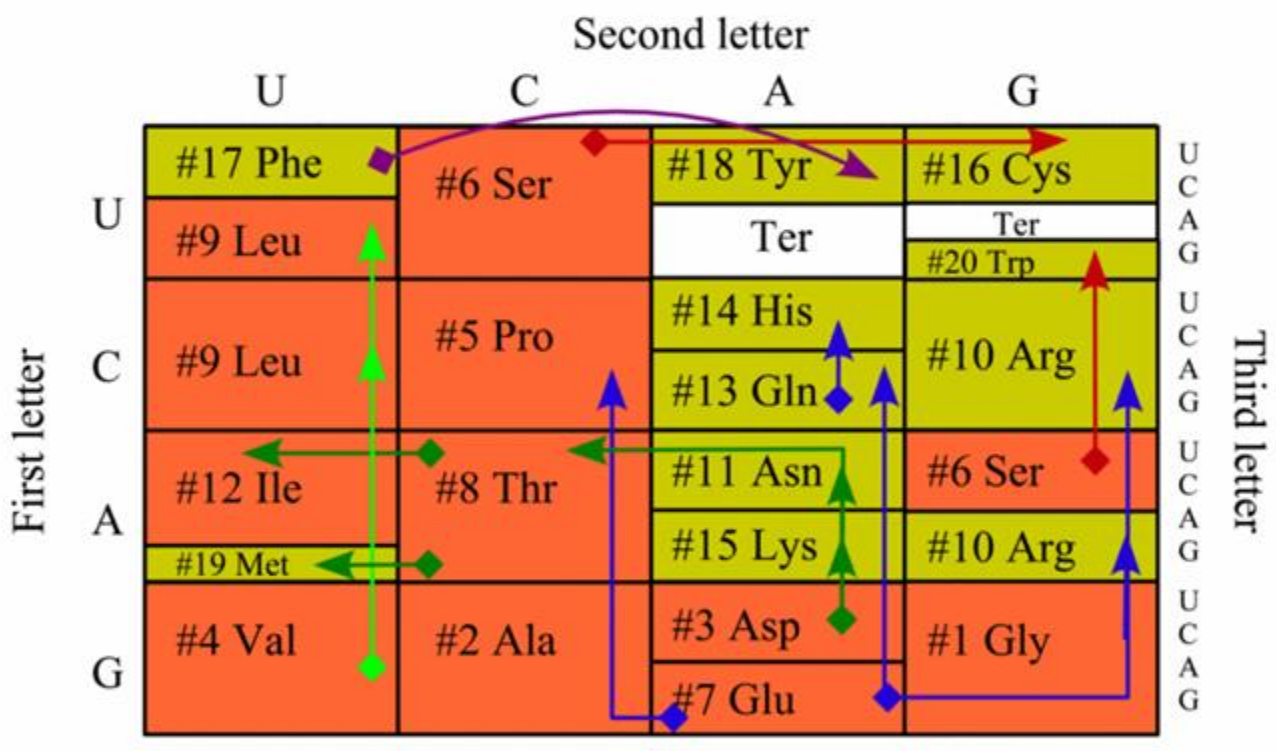


Fig. 4.
The expansion of the standard code according to the coevolution theory. Phase 1 amino acids are orange, and phase 2 amino acids are green. The numbers show the order of amino acid appearance in the code according to (99). The arrows define 13 precursor-product pairs of amino acids, their color defines the biosynthetic families of Glu (blue), Asp (dark-green), Phe (magenta), Ser (red), and Val (light-green)